Significance of cardiac autonomic neuropathy in risk stratification of Brugada syndrome

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Aims Risk stratification in Brugada syndrome (BS) is controversial especially in asymptomatic individuals. The aim of this study was to evaluate the significance of cardiac autonomic neuropathy (CAN) in BS.

Methods and results Patients diagnosed with Brugada ECG pattern were enrolled in the study. Four standard cardiac autonomic function tests were performed. The presence of ≥2 abnormal test results were considered definite evidence for the presence of CAN. Types 1, 2, and 3 Brugada ECG pattern were found in 28, 56, and 31 patients, respectively. CAN was detected in 13 (46%) patients with type 1 Brugada ECG pattern. In contrast, none of the type 2 or 3 Brugada patients had CAN. Of 13 patients with CAN, 11 had previous history of cardiac events (84%), whereas only 2 of 15 patients without CAN had history of previous cardiac events (13%; P = 0.01). The most noteworthy finding was that all of the type 1 Brugada patients with CAN were male (CAN was not detected in females).

Conclusions It was concluded that CAN is an important risk indicator in BS. CAN is more common in men. Male gender, per se, is not an independent risk factor for development of ventricular arrhythmia but also CAN, which is an important risk factor in BS, is more common in men; therefore men are susceptible to the development of cardiac events.

KEYWORDS Arrhythmia; Brugada syndrome; Cardiac autonomic neuropathy

Introduction

Brugada syndrome (BS) is characterized by a coved-type ST-segment elevation in leads V₁ to V₃ and a high incidence of ventricular tachycardia/fibrillation, syncope, and sudden cardiac death in structurally normal hearts.¹⁻¹¹ The clinical characteristics and the variability of the typical ECG features under autonomic modulation indicate the potential role of the cardiac autonomic nervous system in the pathogenesis and arrhythmogenesis of BS.¹² Cardiac autonomic neuropathy (CAN) can be assessed using simple non-invasive tests: the Valsalva manoeuvre, beat-to-beat heart rate variation, postural fall in blood pressure, and the sustained handgrip test. To date, there is no published report regarding clinical evaluation of CAN in BS. Clinical evaluation of CAN in BS is the aim of the present study.

Methods

Study population

Between September 2004 and October 2006, patients referred to the Arrhythmia Clinic in southern Iran¹ and diagnosed with Brugada ECG pattern were enrolled in the study and were given informed written consent. A 12-lead ECG (at a paper speed of 25 mm/s and 1 mV/10 mm standard gain) was recorded from each subject. All ECG recordings were evaluated by two cardiologists. Brugada type ECG pattern was defined as type 1, 2, or 3. Type 1 pattern has coved ST-segment elevation of 2 mm or greater, followed by an inverted Twave, with little or no isoelectric separation. Type 2 pattern also has a high-takeoff ST-segment elevation of 2 mm or greater with gradually descending ST-segment elevation (remaining ≥1 mm above the baseline), followed by a positive or biphasic T wave resulting in a saddleback configuration. Type 2 pattern has either coved or saddleback appearance with right precordial ST-segment elevation of <1 mm.¹³ Type 1 pattern is diagnostic of the Brugada sign, whereas patterns of types 2 and 3 require conversion to the type 1 pattern after challenge with a sodium channel blocking agent to be diagnostic.¹³ If the standard 12-lead ECG showed type 2 or 3 Brugada pattern, 10 mg/kg of procainamide was intravenously administered in 10 min, with the patient being continuously monitored in the intensive care unit. Type 2 and 3 patterns require conversion to the type 1 pattern after challenge with a sodium channel blocking agent to be diagnostic.

Clinical evaluation of cardiac autonomic neuropathy

Four standard cardiac autonomic function tests¹⁴ were performed in the morning after the patients had fasted overnight. To avoid possible confounding factors, patients refrained from physical exercise and partaking of alcohol, caffeine, cigarettes and cigars, and...
variables were compared using Chi-squared test. Group differences in numeric variables were compared using t-test.

From 13 patients with CAN, 11 had history of previous cardiac events (84%) (seven had syncope, three had ventricular tachycardia/fibrillation based on implantable cardioverter defibrillator (ICD) analysis, and three had aborted sudden death). Type 2 and 3 ECG patterns were found in 56 and 31 patients, respectively.

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy was detected in 13 (46%) patients with type 1 Brugada ECG pattern. In contrast, none of the type 2 or 3 Brugada patients have CAN. Characteristics of type 1, 2, and 3 Brugada patients are listed in Table 1. None of the type 1, 2, or 3 patients were taking drugs or anti-arrhythmics that may have affected the autonomic testing.

Characteristics of type 1 Brugada patients with cardiac autonomic neuropathy

From 13 patients with CAN, 11 had history of previous cardiac events (84%) (seven had syncope, three had aborted sudden cardiac death, and one had ventricular fibrillation on ICD analysis), whereas only 2 of 15 patients without CAN had history of previous cardiac events (13%) (Fisher’s exact test: \( P = 0.01 \) (Table 2). The most noteworthy finding was that all of the type 1 Brugada patients with CAN were male (CAN was not detected in females) (Table 3). Details of autonomic testing of the types 1, 2, and 3 Brugada patients are listed in Table 4. Association between each of the four autonomic testing and previous cardiac events in type 1 Brugada patients is illustrated in Table 5. It is obvious that abnormal postural blood pressure and abnormal handgrip tests (which are indicators of sympathetic dysfunction) are significant predictors of previous cardiac events in type 1 Brugada patients.

Discussion

Brugada syndrome and cardiac autonomic neuropathy

The pathophysiology of BS is still under investigation. Interestingly, unlike other diseases, ventricular fibrillation and sudden death mainly occurs in the resting state, predominantly during sleep. The typical ECG changes are variable over time and can be modulated by exercise or pharmacological interventions that interact with the cardiac autonomic innervations. The clinical characteristics and the variability of the typical ECG features under autonomic modulation indicate the potential role of the cardiac autonomic nervous system in the pathogenesis and arrhythmogenesis of BS.

Potential mechanisms of autonomic dysfunction in Brugada syndrome

Increased sympathetic activity has been demonstrated in patients with idiopathic right ventricular outflow tract tachycardia and arrhythmogenic right ventricular cardiomyopathy. In these conditions, however, ventricular tachyarrhythmia is frequently capable of being provoked by exercise or catecholamine and of being suppressed by anti-adrenergic therapy. In contrast, in the BS, ventricular arrhythmias and sudden death occurs mainly at rest or during sleep, suggesting parasympathetic dominance to be a triggering factor. Moreover, ST-segment elevation is augmented by \( \beta \)-blockade or parasympathetic stimulation, whereas it diminishes or disappears with \( \beta \)-adrenergic stimulation. For these reasons, increased sympathetic activity appears to be very unlikely as a mechanism of CAN in BS. Decreased sympathetic activity, as assessed by \( ^{123} \text{I-MIBG-SPECT} \) imaging, has been shown in patients with BS. In patients with BS, however, a reduced adrenergic

| Table 1 Characteristics of patients with type 1, 2, and 3 Brugada electrocardiographic pattern |
|-----------------|-----------------|------------------|-----------------|
|                 | Type 1 \( (n = 28) \) | Type 2 \( (n = 56) \) | Type 3 \( (n = 31) \) |
| Age             | 31.3 ± 11.7      | 30.2 ± 10.2      | 30.6 ± 11.3      |
| Male            | 16 (57%)         | 30 (53%)         | 18 (58%)         |
| Syncope         | 7                | 0                | 0                |
| Ventricular tachycardia/fibrillation | 3                | 0                | 0                |
| Aborted sudden cardiac death | 3                | 0                | 0                |
| Cardiac autonomic neuropathy | 13 (46%)        | 0                | 0                |

NS, non-significant.
Significance of cardiac autonomic neuropathy in risk stratification of Brugada syndrome

In the present study, we found that CAN is present only in type 1 Brugada ECG pattern and none of type 2 or 3 Brugada patients express evidence of CAN. This finding can explain why type 2 or 3 Brugada patients never experience ventricular arrhythmias and these ECG patterns are considered as normal variations. On the other hand, presence of CAN in 46% of type 1 Brugada patients can explain the higher propensity of ventricular arrhythmias in these patients. In the present study, in a retrospective manner, we also showed a significant association between CAN and occurrence of previous cardiac events in patients with type 1 Brugada ECG pattern. Therefore, CAN may be a risk indicator in patients with BS. We also showed that abnormal postural blood pressure and abnormal handgrip tests (which are indicators of sympathetic dysfunction) are significant predictors of previous cardiac events in type 1 Brugada patients.

**Brugada syndrome, male sex, and cardiac autonomic neuropathy**

It is well known that male gender is an important risk factor for ventricular arrhythmias and sudden death in BS and men had a five-fold higher risk of sudden death than did women. The exact mechanism(s) of such association is not well described. The basis for this intriguing sex-related distinction was the subject of a recent experimental study showing that the presence of a more prominent transient outward current (\(I_{\text{to}}\)) in males underlies their predisposition to development of the Brugada phenotype. The less prominent \(I_{\text{to}}\) in females was due in large part to more rapid inactivation kinetics of the channel in females.

Although most families thus far described display a male predominance in the manifestation of BS, a recent study...
by Hong et al.\textsuperscript{20} highlights a family with a female predomi-

nance. The mutation identified, R367H, was the same one previously 
described as a SUDS mutation in a family display-
ing a strong male predominance of the Brugada phenotype. 
This observation suggests that factors other than a specific 
mutation determine the gender distinction.

The most noteworthy finding of the present study was that 
all of the type 1 Brugada patients with CAN were male (CAN 
was not detected in females). In the present study, 13 from 
28 (46\%) of the type 1 Brugada patients had CAN. Of 13 
patients with CAN, all were male (100\%). Therefore, the 
higher incidence of ventricular arrhythmias in men may be 
due to the higher incidence of CAN in men. This finding is 
supported by the fact that men in whom CAN was absent 
never experience previous cardiac events in this study. 
Therefore, we postulate that male gender, per se, is not 
an independent risk factor for development of ventricular 
arrrhythmia but also CAN, an important risk factor in BS, 
is more common in men; therefore men are susceptible to 
the development of cardiac events.

Conclusion

It is concluded that CAN is an important risk indicator in BS. 
CAN is more common in men. Male gender, per se, is not an 
independent risk factor for development of ventricular 
arrrhythmia but also CAN, which is an important risk factor 
in BS, is more common in men; therefore men are suscep-
tible to development of cardiac events.

Conflict of interest: none declared.

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