High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia

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BACKGROUND Atrioventricular nodal reentrant tachycardia (AVNRT) may coexist with Brugada syndrome (BrS).

OBJECTIVES The present study was designed to determine the prevalence of drug-induced type 1 Brugada ECG pattern (concealed BrS) in patients presenting with clinical spontaneous AVNRT and to investigate their electrocardiographic, electrophysiological, and genetic characteristics.

METHODS Ninety-six consecutive patients without any sign of BrS on baseline electrocardiogram undergoing electrophysiological study and ablation for symptomatic, drug-resistant AVNRT and 66 control subjects underwent an ajmaline challenge to unmask BrS. Genetic screening was performed in 17 patients displaying both AVNRT and BrS.

RESULTS A concealed BrS electrocardiogram was uncovered in 26 of 96 patients with AVNRT (27.1%) and in 3 of 66 control subjects (4.5%) ($P \leq .001$). Patients with concealed BrS were predominantly female patients (n = 23 [88.5%] vs n = 44 [62.9%], $P = .015$), had higher prevalence of chest pain (n = 10 [38.5%] vs n = 13 [18.6%], p = 0.042), migraine headaches (n = 10 [38.5%] vs n = 10 [14.2%], p = 0.008), and drug-induced initiation and/or worsening of duration and/or frequency of AVNRT (n = 4 [15.4%] vs n = 1 [1.4%], p = 0.006) as compared to patients with AVNRT without BrS. Genetic screening identified 19 mutations or rare variants in 13 genes in 13 of 17 patients with both AVNRT and BrS (yield = 76.5%). Ten of these 13 genotype-positive patients (76.9%) harbored genetic variants known or suspected to cause a loss of function of cardiac sodium channel current (*SCN5A*, *SCN10A*, *SCN1B*, *GPD1L*, *PKP2*, and *HEY2*).

CONCLUSION Our results suggest that spontaneous AVNRT and concealed BrS co-occur, particularly in female patients, and that genetic variants that reduce sodium channel current may provide a mechanistic link between AVNRT and BrS and predispose to expression of both phenotypes.

KEYWORDS Brugada syndrome; Atrioventricular nodal reentrant tachycardia; Supraventricular tachycardia; Genetics

ABBREVIATIONS **AV** = atrioventricular; **AVNRT** = atrioventricular nodal reentrant tachycardia; **BrS** = Brugada syndrome; **ECG** = electrocardiogram/electrocardiographic; $\mathbf{I_{Na}}$ = sodium channel current; **PSVT** = paroxysmal supraventricular tachycardia

Introduction

Brugada syndrome (BrS) is a form of inherited arrhythmia syndrome characterized by a distinct ST-segment elevation in the right precordial leads in the absence of structural heart disease.[1] BrS can be manifest, suspicious, or concealed on the basis of clinical and electrocardiographic (ECG) characteristics.

BrS has been shown to be associated with atrial arrhythmias such as atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia (PSVT).[2–5] In the presence of increased prevalence of spontaneous and/or inducible atrioventricular nodal reentrant tachycardia (AVNRT) in patients with manifest BrS compared with the general population (7% vs ~0.135%), we hypothesized that spontaneous AVNRT may co-exist with a concealed or manifest BrS phenotype.[4–6] The aim of this study was first to determine the prevalence of concealed BrS in patients presenting with clinical spontaneous AVNRT and second to investigate the clinical, ECG, electrophysiological, and genetic characteristics of these patients.

This study was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (grant no. HL47678, to Dr Antzelevitch) and the Masons of New York, Florida, Massachusetts, Connecticut, Maryland, Delaware, Rhode Island, New Hampshire, and Wisconsin. **Address reprint requests and correspondence:** Dr Can Hasdemir, Department of Cardiology, Ege University School of Medicine, Bornova, Izmir 35100, Turkey. E-mail address: can.hasdemir@yahoo.com.

Methods

Study populations

One hundred three consecutive patients without any signs of the Brugada pattern on baseline standard 12-lead ECGs who underwent electrophysiological study and catheter ablation

for symptomatic, drug-resistant AVNRT between July 2011 and November 2013 were retrospectively included. Seven patients were excluded owing to ischemic cardiomyopathy (n = 3), coexisting concealed accessory pathway (n = 2), secundum-type atrial septal defect (n = 1), and rheumatic heart disease (n = 1). The remaining 96 patients (67 women and 29 men; mean age 46 ± 15 years; range 18–72 years) formed the patient population, and their characteristics were compared with those of the control group (n = 66 [42 women and 24 men]; mean age 42.7 ± 9.5 years; range 25–63 years). All patients and control subjects underwent the ajmaline challenge test. Genetic screening and analysis was performed in a total of 17 patients: 10 with concealed BrS and clinical AVNRT from our present study and 7 with previous diagnosis of BrS and clinical AVNRT from our observational BrS cohort consisting of 71 patients referred to our tertiary referral hospital between January 2004 and December 2013. The study protocol was approved by the ethics committee of the Ege University School of Medicine. Written informed consent was obtained from all patients for ajmaline challenge test and genetic testing.

Data acquisition

A detailed medical history including age of onset of AVNRT, associated symptoms (palpitation, chest pain, syncope, and cardiac arrest), presence of systemic diseases (systemic hypertension, diabetes mellitus, and migraine headaches), and initiation of AVNRT (in the presence of high sympathetic or parasympathetic tone or both) was obtained in all patients. Syncope was classified as reflex (vasovagal or situational), orthostatic hypotension, arrhythmia-related cardiac syncope, and unexplained syncope. The diagnosis of migraine headache was based on the criteria of the International Classification of Headache Disorders, 2nd edition.[7]

Presence of additional atrial (focal atrial tachycardia and atrial fibrillation) and ventricular (frequent [>10 per hour], monomorphic premature ventricular contractions, and/or ventricular tachycardia) arrhythmias, family history of AVNRT (documented AVNRT in ≥ 2 family members), and sudden unexpected death (≤ 50 years of age) in the first-degree relatives were noted in all patients with AVNRT. Brugada pattern–inducing drug exposure and its effect on AVNRT frequency and duration were noted in all patients.

All study subjects underwent transthoracic echocardiography for the evaluation of valves and right and left ventricular size and function.

Definition of ECG parameters

All subjects had a baseline 12-lead ECG with leads in the standard lead position and a high precordial lead ECG, with leads V_1 and V_2 moved up to the third and the second intercostal space.[3] Type 1 Brugada pattern, QRS fragmentation, and early repolarization patterns were defined according to previously described criteria.[8–10]

Every patient had a 12-lead ECG during their index clinical arrhythmia. Twelve-lead ECGs were analyzed for the rate of clinical AVNRT, presence of pseudo-r′ deflection in lead V_1, pseudo-S wave in inferior leads, P-in-QRS pattern (absence of pseudo-r′ deflection in lead V_1 and/or pseudo-S wave in inferior leads), and QRS alternans.[11] Five patients were excluded for the analysis: 3 with slow/slow AVNRT, 1 with fast/slow AVNRT, and 1 with left variant slow/fast AVNRT.

Electrophysiological study

All patients with AVNRT underwent electrophysiological study and catheter ablation. The diagnosis of AVNRT was made on the basis of previously described criteria.[12] Baseline AH and HV intervals, type and rate of AVNRT, time intervals (His-V, V-A_{His}, V-$A_{right\ atrial\ appendage}$, and V-$A_{distal\ coronary\ sinus}$) during AVNRT were determined in each patient.

Definition of BrS

Type 1 Brugada pattern in at least 1 right precordial lead was considered to be diagnostic of BrS.[8] Manifest BrS was defined as the presence of diagnostic type 1 Brugada pattern on baseline 12-lead ECGs before the drug challenge test in the presence of a presenting symptom. Suspicious BrS was defined as the presence of type 2 or 3 Brugada pattern on baseline 12-lead ECGs before the drug challenge test in the presence of a presenting symptom. Concealed BrS was defined as the absence of any signs of Brugada pattern on baseline 12-lead ECGs before the drug challenge test and the development of type 1 Brugada pattern after the drug challenge test regardless of symptomatic status, consistent with the current guidelines.[8]

Definition of the control group

The control group consisted of unrelated subjects with structurally normal hearts and no history of any type of atrial arrhythmia including AVNRT, premature ventricular contractions, or ventricular tachycardia.

Ajmaline challenge test

The ajmaline challenge test was performed according to the second BrS consensus conference report.[3] Ajmaline was administered as continuous intravenous infusion at a rate of 1 mg/kg bodyweight over 5 minutes. Criteria for discontinuation of ajmaline infusion were the development of diagnostic type 1 Brugada pattern, ventricular arrhythmias, and QRS widening to $\geq 130\%$ of baseline. Patients with AVNRT underwent an ajmaline challenge after electrophysiological study and catheter ablation. All tests were performed by the same investigator in the same center using the same equipment with the same standard settings. Twelve-lead ECGs were recorded by using a standard electrocardiograph (ECG-9132K, Nihon Kohden Corporation, Nakano-Ku, TKY, Japan) with standard settings (paper speed 25 mm/s and gain setting 10 mm/mV) in all subjects. PR and corrected QT intervals, QRS duration, and QRS axis were automatically