

A patient with sick sinus syndrome, atrial flutter and bidirectional ventricular tachycardia: Coincident or concomitant presentations?

Amir Farjam Fazelifar¹, Mohammad Hosein Nikoo², Majid Haghjoo¹, Zahra Emkanjoo¹, Abolfath Alizadeh¹, Hamid Reza Bonakdar¹ and Mohammad Ali Sadr-Ameli¹

¹Pacemaker and Electrophysiology Department,

Rajaie Cardiovascular Medical and Research Centre, Teheran, Iran

²Pacemaker and Electrophysiology Department, Kosar General Hospital, Shiraz, Iran

Abstract

Channelopathies are among the major causes of syncope or sudden cardiac death in patients with structurally normal hearts. In these patients, the atrium, ventricle or both could be affected and reveal different presentations. In this case, we present a patient with an apparently structurally normal heart and recurrent syncope, presented as sick sinus syndrome with atrial flutter and bidirectional ventricular tachycardia. (Cardiol J 2007; 14: 585–588)

Key words: syncope, sick sinus syndrome, bidirectional ventricular tachycardia

Introduction

Channelopathies are among the major causes of syncope in patients with structurally normal hearts and may have different presentations [1]. The atrium, ventricle or both could be affected by the channelopathies, and arrhythmia in each chamber may cause syncope [2]. Physicians should notice the appearance of new arrhythmia in patients with recurrent syncope and channelopathies. In this case, we present a patient with recurrent syncope and an apparently structurally normal heart, presented as sick sinus syndrome (SSS) with atrial flutter and bidirectional ventricular tachycardia.

Address for correspondence:
Amir Farjam Fazelifar, MD
Pacemaker and Cardiac Electrophysiology Department
Rajaie Cardiovascular Medical and Research Centre
Mellat Park, Vali-E-Asr Avenue
P.O. Box: 15745-1341, Tehran, 1996911151, Iran
e-mail: fazelifar@gmail.com
Tel: 0098 21 2392 2931, fax: 0098 21 2204 8174
Received: 9.05.2007 Accepted: 16.06.2007

Case report

Interrogatory

A 24-year-old woman presented with frequent episodes of unexplained syncope. Occasional episodes of chest discomfort before syncope were reported by the patient.

Familial background

One of her cousins on her father's side had died suddenly. This information was extracted from her medical file. Physical examination was unremarkable.

Electrocardiogram showed relative sinus bradycardia without any evidence of conduction abnormalities, ST-segment elevation in right precordial leads and QT prolongation. We did not find significant U wave alteration.

Echocardiography revealed normal right and left ventricular size and function. Occasional episodes of chest discomfort before syncope were reported by the patient. Right and left cardiac catheterization and coronary angiography showed no abnormality. Brain computed tomographic scan and electroencephalogram were normal. Head-up tilt table test was negative. The key to diagnosis was

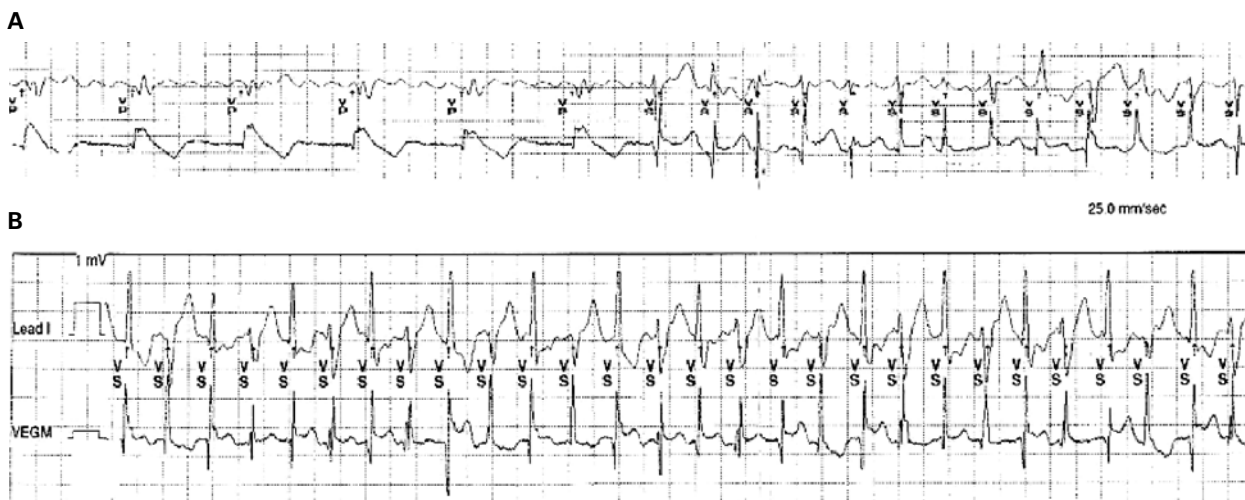


Figure 1. Initiation of spontaneous polymorphic ventricular tachycardia (A) converted to bidirectional VT (B). Please notice the atrial flutter with ventricular paced rhythm.

the last 24-hour Holter monitoring. She reported palpitation and dizziness, concomitant with atrial flutter and a five-second pause after termination during Holter monitoring. The patient became a candidate for electrophysiological study and arrhythmia radiofrequency (RF) ablation. The procedure was refused by the patient. Antiarrhythmic drug therapy (flecainide, 50 mg PO bid) started, and a dual chamber pacemaker (Kappa KDR701, Medtronic Inc, Minneapolis, USA) was implanted. In the first year of follow up the patient was symptom-free with no recurrence of syncope. She did not return for pacemaker analysis and stopped taking the drug of her own volition. She developed recurrent syncope during the second year of follow up; pacemaker analysis was normal and programmed to VVIR mode because of persistent atrial flutter. The patient referred for arrhythmia RF ablation. During pacemaker analysis in our clinic, a spontaneous episode of bidirectional ventricular tachycardia due to emotional stress occurred (Fig. 1).

No drug consumption was reported by the patient. Clinically speaking, catecholaminergic polymorphic ventricular tachycardia (CPVT) strongly suggested for her. After bidirectional isthmus block, the atrial flutter was terminated and sinus rhythm restored, successfully. During a study on isoproterenol for evaluation of bidirectional isthmus block, a spontaneous short episode of nonsustained polymorphic ventricular tachycardia was induced. Her pacemaker was upgraded to a dual chamber implantable cardioverter-defibrillator. Beta-adrenergic blockers are the most effective pharmacological treatment in controlling arrhythmias in CPVT

patients, yet about 30% of patients still experience cardiac arrhythmias and eventually require an implantable cardioverter defibrillator. Beta-blocker was started and increased to maximum tolerated dose. Predischarge exercise tolerance test was normal. The patient was symptom free during six months follow up. Unfortunately, genetic analysis is not available in our country.

Discussion

In patients with structurally normal hearts, channelopathies are one of the most important causes of syncope or sudden cardiac death. Catecholaminergic bidirectional ventricular tachycardia is observed in patients with familial CPVT, a rare arrhythmic syndrome occurring in patients with apparently structurally intact hearts.

Cardiac ryanodine receptor gene (RYR2) is sometimes (not always) responsible for this arrhythmia [3]. Mutations in cardiac ryanodine receptors and calsequestrin genes are responsible for the autosomal dominant and recessive variants of CPVT, respectively.

RyR2 is located on the sarcoplasmic reticulum and controls intracellular Ca^{++} release and muscle contraction and relaxation in the heart by its capacity of fast release and seizure of myoplasm of Ca^{++} ion, as it has just in the unions with the T system of the plasmatic membrane, the so-called Ca^{++} release channel or ryanodine receptor.

Protein kinas phosphorylation dissociates the stabilizing FKBP12.6 subunit (calstabin2) from the RyR2 complex, resulting in increased contractility

and cardiac output. Increased RyR2 phosphorylation and pathologically increased calstabin2 dissociation during exercise results in aberrant diastolic calcium release, which may trigger ventricular arrhythmias and sudden cardiac death [4].

One group has described a missense mutation in a highly conserved region of the calsequestrin 2 gene (CASQ2) as a potential cause of the autosomal recessive form of CPVT [5].

This entity may induce arrhythmic events or arrhythmias at the atrial level. CPVT patients with RyR2 mutation might have bradycardia regardless of the site of the mutation, which could direct molecular diagnosis in young patients without structural heart disease presenting with syncopal attacks and slow heart rate but with normal QTc at resting electrocardiogram [6].

Bassani et al. [7] showed the effect of ryanodine on sinus node recovery time determined in vitro. These results indicate that:

- a functional sarcoplasmic reticulum, albeit important for force development, does not seem to play a major role in atrial automaticity in rats;
- disruption of cell Ca^{++} homeostasis by inhibition of sarcoplasmic reticulum function does not appear to affect conduction; however, it enhances overdrive-induced depression of sinus automaticity.

Another study showed that inactivation of ryanodine receptor reduces, or can abolish, sinoatrial nodal cell automaticity [8]. The biological clock of sinoatrial nodal pacemaker cells, like that of many other rhythmic functions occurring throughout nature, involves an intracellular Ca^{2+} rhythm.

Interestingly, in a patient, simultaneous over-activation and inactivation of a gene mutation have been reported. Beaufort-Krol et al. [9] published different aspects of a single gene SCN5A mutation. They concluded that electrocardiographic characteristics of LQT3 and Brugada syndrome show age-dependent penetrance. A QT prolongation and conduction disease were present from birth onwards, whereas ST-segment elevation only developed after 5 years. LQT3 is consistently caused by increased net Na current secondary to inactivation defects, which gives rise to persistent Na current during phase 2. Conversely, various gating changes that ultimately result in reduced Na current may elicit Brugada syndrome, conduction disease, atrial standstill and sinus node disease.

We could not find simultaneous gain and loss of ryanodine receptor function in a patient in the literature. During calcium-induced calcium-release, the ryanodine receptor (RyR) opens and releases

large amounts of calcium from the sarcoplasmic reticulum into the cytoplasm of the myocyte. Recent experiments have suggested that cooperativity between the four monomers comprising the RyR plays an important role in the dynamics of the overall receptor. Furthermore, this cooperativity can be affected by the binding of FK506 binding protein, and hence, modulated by adrenergic stimulation through the phosphorylating action of protein kinase A. This has important implications for heart failure, where it has been hypothesized that RyR hyperphosphorylation, resulting in a loss of cooperativity, can lead to a persistent leak and reduced sarcoplasmic-reticula content.

Conclusions

To our best knowledge, this is the first reported case of bidirectional ventricular tachycardia in which sick sinus syndrome and atrial flutter was observed. In patients with recurrent syncope and a normal heart, different clinical presentations of a single gene mutation and/or the presence of more than one gene mutation should be expected. The molecular diagnostics of CPVT have become increasingly important because the underlying mutations can be found in more than 60% of identified CPVT patients. Along with the fact that treatment with beta-blockers has a favourable outcome in CPVT patients, and given the risk of sudden death, the identification of causative mutations in CPVT is important because it can greatly augment early diagnosis and subsequent preventive strategies.

References

1. Sumiyoshi M, Nakazato Y, Tokano T et al. Sinus node dysfunction concomitant with Brugada syndrome. *Circ J*, 2005; 69: 946–950.
2. Van Den Berg MP, Wilde AM, Viersma JW et al. Possible bradycardia mode of death and successful pacemaker treatment in a large family with features of long QT syndrome type 3 and Brugada syndrome. *J Cardiovasc Electrophysiol*, 2001; 12: 630–636.
3. Priori SG, Napolitano C, Memmi M et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*, 2002; 106: 69–74.
4. Lenhart SE, Wehrens XH, Kushnir A, Marks AR. Cardiac ryanodine receptor function and regulation in heart disease. *Ann NY Acad Sci*, 2004; 1015: 144–159.
5. Lahat H, Pras E, Olender T et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholaminergic-induced

- polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet*, 2001; 69: 1378–1384.
6. Postma AV, Denjoy I, Kamblock J et al. Catecholaminergic polymorphic ventricular tachycardia: RyR2 mutations, bradycardia and follow up of the patients. *J Med Genet*, 2005; 42: 863–870.
 7. Bassani JW, Godoy CMG, Bassani RA. Effect of ryanodine on sinus node recovery time determined *in vitro*. *Braz J Med Biol Res*, 1999; 32: 1039–1043.
 8. Bogdanov KY, Vinogradova TM, Lakatta EG. Sinus nodal cell ryanodine receptor and Na⁺-Ca²⁺ exchanger, molecular partners in pacemaker regulation. *Circ Res*, 2001; 88: 1254–1258.
 9. Beaufort-Krol GC, van den Berg MP, Wilde AA et al. Developmental aspects of long QT syndrome type 3 and Brugada syndrome on the basis of a single SCN5A mutation in childhood. *J Am Coll Cardiol*, 2005; 46:331–337.