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Sudden cardiac arrest due to a single sodium channel mutation producing a mixed phenotype of Brugada and Long QT3 syndromes

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ABSTRACT

Inherited arrhythmia syndromes are a known, albeit rare, cause of sudden cardiac arrest which may present with characteristic electrocardiogram changes in patients with structurally normal heart. There are a variety of distinct arrhythmogenic syndromes that arise from mutations in voltage gated sodium channels, resulting in either gain or loss of function. We describe a patient with a primary inherited arrhythmia syndrome which presented as sudden cardiac arrest. Further workup revealed that her arrest was due to a combination of Brugada syndrome and Long QT3 syndrome secondary to a deleterious mutation of voltage-gated, sodium channel, type V alpha subunit (SCN5A Thr1709Met).

1. Introduction

Inherited arrhythmia syndromes may cause sudden cardiac arrest (SCA) in patients with a structurally normal heart. These inherited arrhythmia syndromes usually present with characteristic electrocardiogram (ECG) appearances. Mutations in the voltage gated sodium channel can produce distinct arrhythmogenic syndromes: Brugada syndrome (BrS), Long QT3 syndrome (LQT3) and Progressive cardiac conduction disease. Mutations in BrS are those of the loss in function of the sodium channel, whereas the mutations in the LQT3 are those of the gain in the function of sodium channel. However, rarely a single gene mutation can present with a phenotype overlap syndrome - both BrS and LQT3 in a same patient. We present a case of primary inherited arrhythmia syndrome due to a deleterious mutation of voltage-gated, sodium channel, type V alpha subunit (SCN5A) Thr1709Met leading to a combination of BrS and LQT3.

1.1. Case presentation

A 57 year-old female collapsed in her kitchen and was subsequently found to be pulseless by family, who initiated bystander CPR. EMS arrived after seven minutes and found her in shockable rhythm. She received a total of six shocks and continued to have recurrent ventricular tachyarrhythmia. She was treated with IV lidocaine as a bolus. She had return of spontaneous circulation after 32 minutes of ACLS. Past medical history was significant for hypertension, depression and hypothyroidism. Medications included citalopram 20 mgs, thyroxine 88mcg, lisinopril 10 mgs and hydrochlorothiazide 25 mgs daily. Family history was significant for SCA of her maternal uncle at the age of 40. She had no history of recreational drug use. Vitals after initial resuscitation were as follows: BP 100/60 mmHg, Pulse 98/min. Physical examination was unremarkable. Admission ECG showed sinus tachycardia, nonspecific ST-T changes and QTc interval of 503 msec (Fig. 1A).

Blood chemistry showed potassium of 3.8 mEq/L and peak troponin of 2.9 ng/ml. Echo revealed global left ventricular systolic function with an estimated left ventricular ejection fraction of 30% and normal right ventricular function. Normal coronary arteries were found on cardiac catheterization. She was started on mild induced therapeutic hypothermia (Temp of 32–33 °C) protocol after resuscitation. Her QTc prolonged to 630 msec with a long isoelectric segment between the QRS and T wave during the peak of hypothermia protocol when her baseline heart rate was 50 bpm (Fig. 1B). After the completion of hypothermia protocol, her ECG showed prominent coved ST segment elevation of 3 mm in the right precordial leads followed by T wave inversion (Fig. 2A). QRS duration in the right precordial leads was longer when compared to the left precordial leads. QT dispersion was 60 msec (Fig. 2B). Her potassium at that time was 4.1 mEq/L and magnesium was 1.9 mg/dl.

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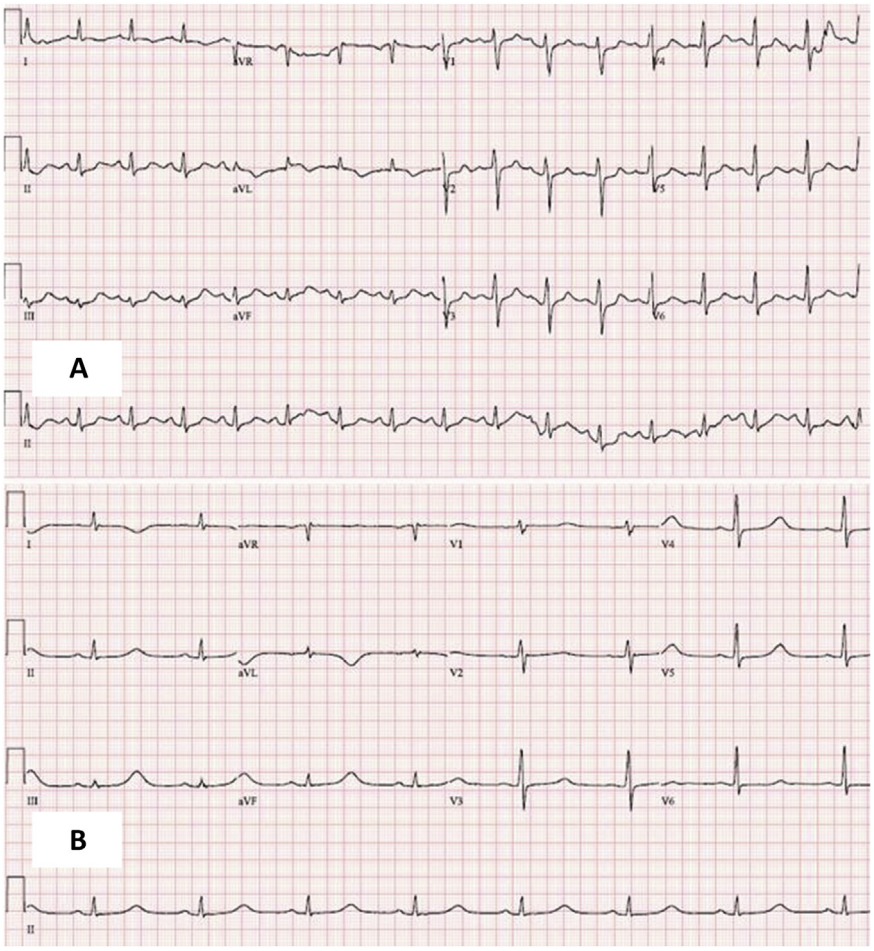

Fig. 1. **A**: Admission ECG, sinus tachycardia, nonspecific ST-T changes, QTc 503 msec. **B**: QTc interval 630 msec, long isoelectric segment between QRS and T wave.

That night, she started having multiple episodes of ventricular fibrillation (VF) (Fig. 2C) requiring 18 defibrillation shocks. Her core body temperature was 36.2 °C at that time. Her VF storm was treated with isoproterenol infusion, followed by oral quinidine 400mg three times a day, with good control of her VF. After four weeks, she was reevaluated in office and noted to have petechial rashes in the extremities and oral cavity. Complete blood count showed platelet count of 5000/μL. Further evaluation was consistent with drug induced idiopathic thrombocytopenic purpura. She was treated with steroids and IV immunoglobulin with improvement in platelet count. Her quinidine was discontinued and she started having short runs of *torsades de pointes* (TDP) (Fig. 2D).

She was then started on disopyramide 150 mg q8h and up titrated to 300 mg q8h, which was tolerated well with no recurrence of TDP. Her baseline ECG (Fig. 3) showed normal QTc interval (437 msecs) and type 2 Brugada pattern. Her follow up ECG showed normal QTc interval. She later tested positive for class I deleterious mutation of SCN5A Thr1709Met (Fig. 4), which has been associated with prior cases of BrS. (http://www.transgenomic.com/product/famillion-brs/; accessed on 11/4/2015). This is the first reported case of SCN5A Thr1709 missense mutation which presented as a phenotypic overlap between BrS and LQT3.

2. Discussion

We report a rare case of sudden cardiac arrest due to a combination of BrS and LQT3 syndrome secondary to deleterious mutation of SCN5A Thr1709Met. Mutations in SCN5A have been associated with at least three forms of primary electrical disorders, namely LQTS3, BrS and progressive cardiac conduction defects [1]. Mutations in BrS are those of the loss in function of the sodium channel during the phase 0 of the cardiac action potential, whereas the mutations in the Long QT3 syndrome are those of the gain in the function of sodium channel which is responsible for phase 2 of the cardiac action potential. A single SCN5A insertion mutation presenting with features of both BrS and LQT3 syndrome had been reported [2]. This mutation produces an early sodium channel closure, but augments the late sodium channel current due to a slower recovery of the sodium channels from inactivation.

The cardiac Na^+ channel α-subunit (SCN5A) is composed of four homologous domains, DI–DIV (Fig. 4). In each domain, the S1–S4 segments serve as the voltage-sensing module, and the S5 and S6 segments and the reentrant loop between them serve as the pore-forming module which is important for sodium inactivation. During the Phase 1 of cardiac action potential, I_{Na} rapidly enters inside the cell. Fast inactivation of the sodium channel is a critical process that occurs within milliseconds of channel opening. The latch of this fast inactivation gate (between S5 and S6 segments) is formed by three key hydrophobic residues, isoleucine, phenylalanine, and methionine, and an adjacent threonine (T). Any mutation involving these channels could produce incomplete inactivation of $I_{Na,}$ resulting in a slow and constant entry of sodium during phase II of the action potential and hence prolong QT interval [1].

Our patient initially displayed significant QTc prolongation with