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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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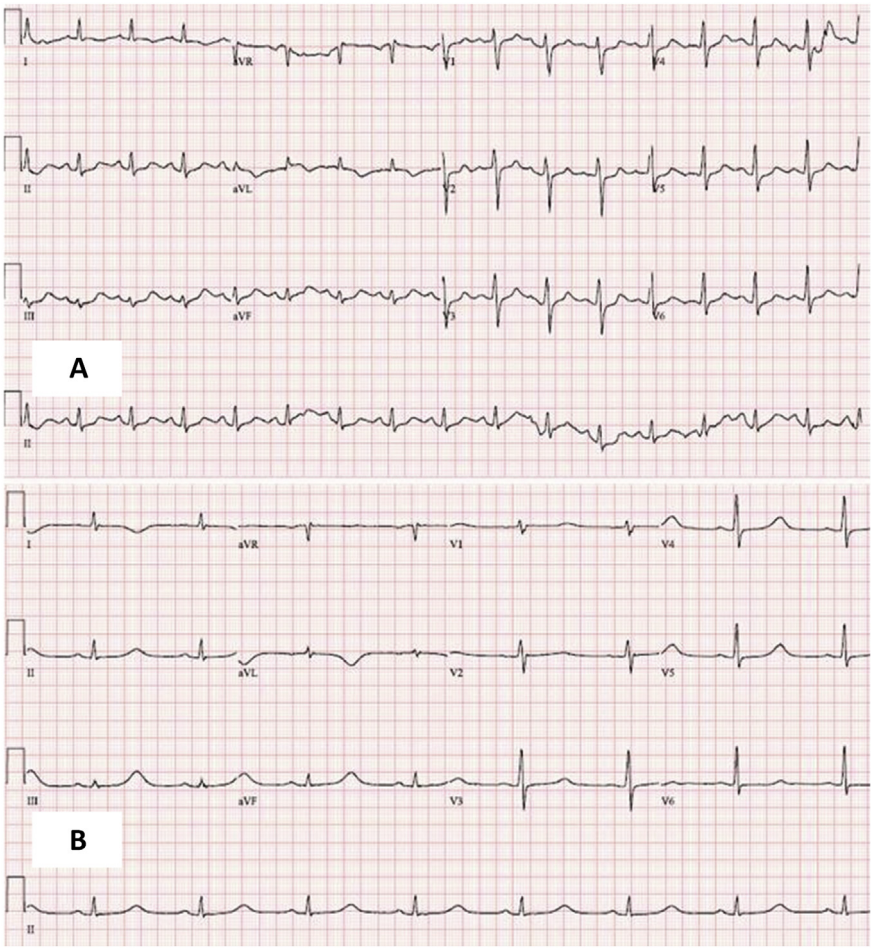

Fig. 1. **A**: Admission ECG, sinus tachycardia, nonspecific ST-T changes, QTc 503 msec. **B**: QTc interval 630 msec, long isoelectric segment between QRS and T wave.

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

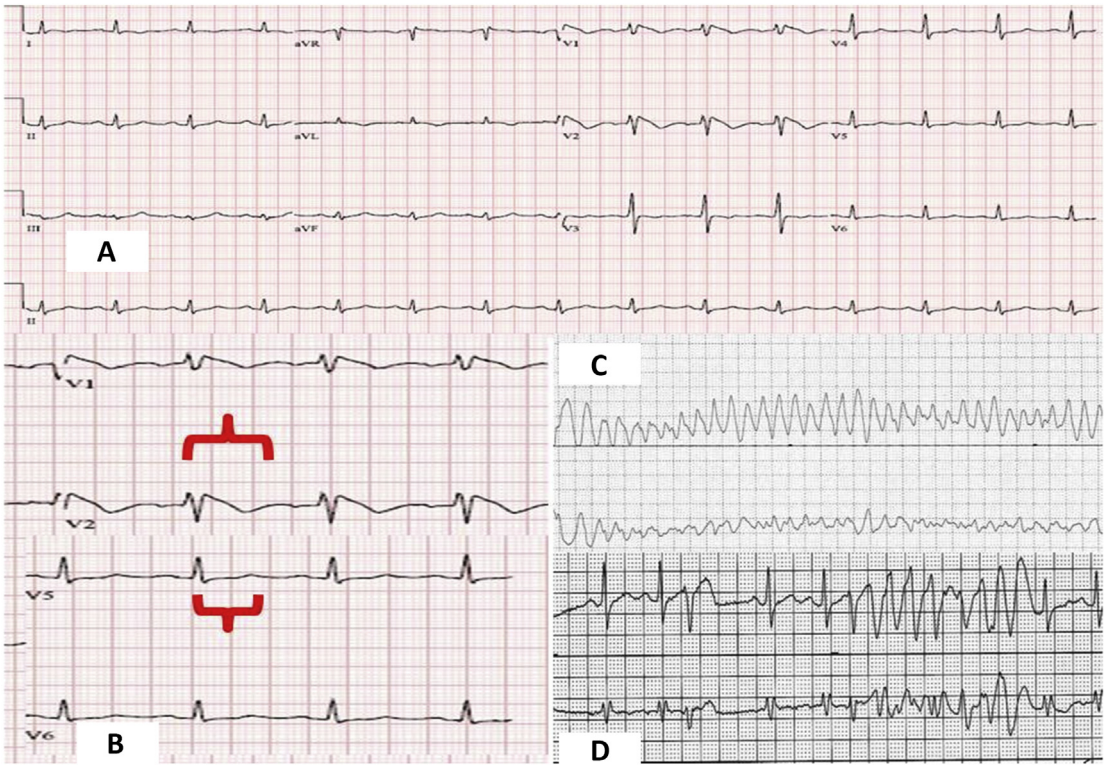

Fig. 2. **A**: Prominent ST elevation followed by T wave inversion in right precordial leads. **B**: QT dispersion in precordial leads. **C**: *Torsades de pointes* degenerating in to Ventricular fibrillation. **D**: Shorts runs of *Torsades de pointes*.

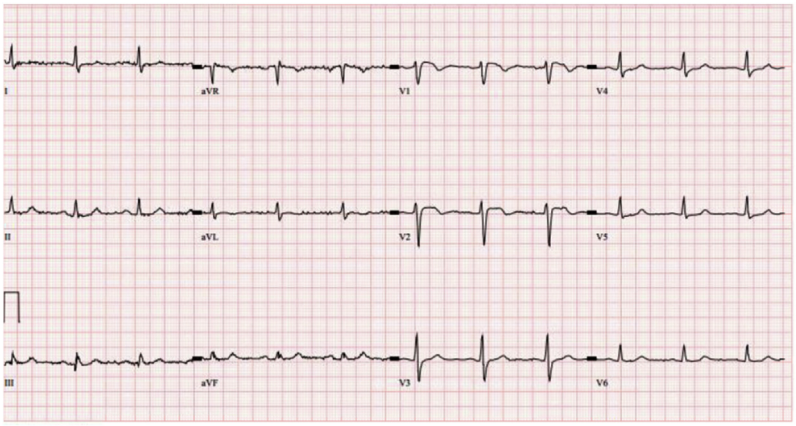

Fig. 3. Baseline pre -event ECG showing type 2 Brugada pattern and normal QTc interval.

a long isoelectric segment between the QRS and T wave during the peak of hypothermia protocol. It is well known that Citalopram could produce QTc prolongation in a dose dependent manner. Recently, both the manufacturer of Citalopram and the US Food and Drug Administration have warned about drug-induced QTc interval prolongation and torsades de pointes when using citalopram in doses >40 mg/day. Our patient was using Citalopram 20 mg daily, and less likely to be the cause for QTc prolongation. It is possible that incomplete inactivation of I_{Na} as a result of mutation in the SCN5A gene likely contributed to abnormal repolarization at slow rates [3]. Thus, bradycardia associated with hypothermia may have precipitated QT-interval prolongation and abnormal T-wave configuration. LQT3 syndrome is an inherited cardiac arrhythmia that may cause abrupt syncope, seizures and sudden death from ventricular tachyarrhythmias, specifically TDP and VF. In LQT3 patients, a long isoelectric ST segment precedes a peaked T wave.

There is a persistent I_{Na} current during the plateau phase of the action potential, secondary to incomplete inactivation of mutated channels. This in turn leads to prolonged repolarization resulting in the formation of early afterdepolarizations in phase III of the action potential. These early afterdepolarizations trigger ventricular ectopies, which initiate a short-long-short cycle, triggering *torsade de pointes* in an underlying myocardial substrate of increased dispersion of repolarization with partial recovery of action potential, especially in the middle layers (M cell) of myocardium [4]. There is also a marked transmyocardial dispersion due to a slower

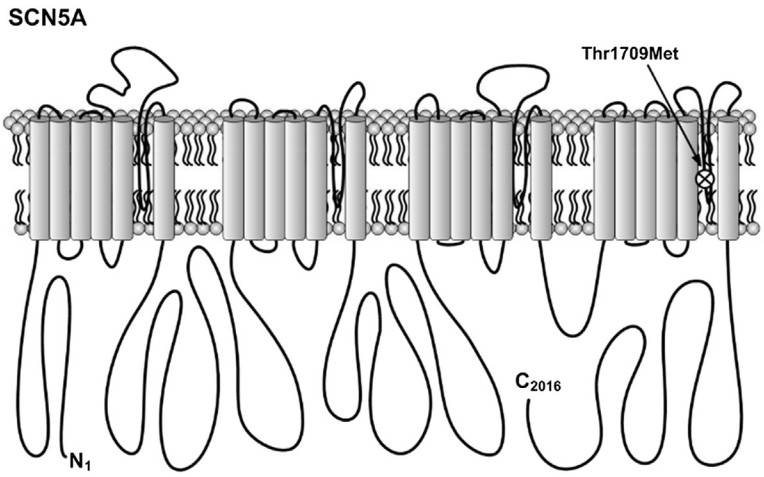

Fig. 4. Missense mutant SCN5A Thr1709. Domain I–IV and Segments 1 to 6 of SCN5A. Thr1709 – Site of mutation between S5 and S6 in our patient.

repolarization in M cells because M cells possess the lowest concentration of slow activating, delayed rectifying IKs current.

Our patient also displayed ST elevation consistent with the diagnosis of BrS after rewarming from hypothermia. BrS is diagnosed by an ECG with ST segment elevation of equal to or more than 2 mm in at least one of the right precordial leads (V1, V2) positioned in the 2nd, 3rd or 4th intercostal space, either occurring spontaneously or after the administration of intravenous sodium channel blockers [5]. Patients may only intermittently display characteristic ECG changes with otherwise normal ECG appearance. ECG abnormalities and arrhythmia induction in the SCN5A-linked forms of BrS involve the imbalance of ionic currents during phase 1 repolarization. The deep phase 1 notch in the epicardial action potential, particularly prominent in the right ventricle, renders it susceptible to the effects of a reduction in the I_{Na+} current. The reduction in I_{Na+} current establishes a steep voltage gradient across the right ventricular wall (leading on to ST-elevation) due to short-circuiting of the epicardial action potential with extreme shortening. The imbalance of currents allows for reactivation of the right ventricular epicardium by neighboring regions of myocardium, with longer action potentials producing functional reentry, referred to as phase 2 reentry [5]. QT intervals have been reported to be normal in patients with BrS[7]. Patients who have QTc prolongation in the setting of BrS should raise the suspicion of associated genetic variation. Genetic testing could be of help in borderline cases or in cases where a new mutation is suspected.

The objective of medical management of VF storm due to BrS is to use drugs that inhibit the transient outward potassium current (Ito) or increase the sodium and calcium currents. Isoproterenol increases the L-type calcium current and proved to be useful for treatment of electrical storm in the setting of BrS [5]. Quinidine, which blocks Ito and Ikr currents, has been shown to prevent induction of VF and suppress spontaneous ventricular arrhythmias [5]. Use of disopyramide (due to Ito-suppressing effect) to treat VF storm in BrS has also been reported [5]. The administration of cilostazol may have a beneficial effect in patients with the Brugada syndrome by mediating an increase in calcium current and reduction in I(to) due to an increase in heart rate [5]. Bepridil, a class III drug with Ito blocking properties, is reported to be effective in treating BrS patients with frequent VF recurrences, but the drug is only available in Japan. In symptomatic patients with LQT3 syndrome where the *torsade de pointes* is either bradycardia or pause-dependent, a pacemaker is used to avoid bradycardia and pauses. Although beta-adrenergic blockers are used in the chronic treatment of LQT syndrome in general, these agents are used with caution in patients with LQT3 syndrome, especially with resting bradycardia since further reduction in heart rate by beta-adrenergic blockers theoretically may provoke TDP. Ranolozine and Mexiletine may be used in patients with LQT3 syndrome due to their late I_{Na} blocking effects.

In a patient with sudden cardiac arrest, certain clinical features can point towards a SCN5A mutation: a long isoelectric ST segment preceding a peaked T wave (LQT3); longer QTc interval in lead V2, exercise induced ST segment elevation; long sinus pauses and prolongation of P, PR interval or QRS widening with left axis deviation (PCCD) [1]. Therefore, evaluating the previous baseline ECGs cannot be overemphasized.

3. Conclusion

The combination of ECG features suggesting LQT3 and BrS ECG should make one think about the SCN5A mutation, which can facilitate treatment strategy in addition to genetic screening of family members.

Conflict of interest

None.

Disclosure

None.

References

[1] Bezzina CR, Rook MB, Wilde AA. Cardiac sodium channel and inherited arrhythmia syndromes. Cardiovasc Res 2001;49(2):257–71. doi: S0008636300002728 [pii].
[2] Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, et al. A single na(+) channel mutation causing both long-QT and brugada syndromes. Circ Res 1999;85(12):1206–13.
[3] Schwartz PJ, Priori SG, Locati EH, Napolitano, C, Cantu F, Towbin JA, et al. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to na+ channel blockade and to increases in heart rate. implications for gene-specific therapy. Circulation 1995;92(12):3381–6.
[4] Viskin S, Alla SR, Barron HV, Heller K, Saxon L, Kitzis I, et al. Mode of onset of torsade de pointes in congenital long QT syndrome. J Am Coll Cardiol 1996;28(5):1262–8. doi: S0735109796003117 [pii].
[5] Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace 2013;15(10):1389–406. http://dx.doi.org/10.1093/europace/eut272.