Catheter ablation of ventricular fibrillation storm in a long QT syndrome genotype carrier with normal QT interval

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ABSTRACT Patients with long QT syndrome can sometimes present with a ventricular fibrillation (VF) storm. Catheter ablation of culprit premature ventricular complexes responsible for the triggering of the VF episodes may be required in rare cases of electrical storm that do not respond to conventional measures, and this can be life-saving. We describe a case of emergency catheter ablation in a young woman with a normal corrected QT interval, who presented with malignant VF storm for the first time. We also discuss the diagnostic and management challenges involved, as well as the value of genetic testing in refining the diagnosis.

INTRODUCTION

Long QT syndrome (LQTS) is a well-recognised cause of sudden cardiac death and is usually associated with abnormal ventricular repolarisation evident on resting 12-lead electrocardiography (ECG). However, in up to 25% of patients with LQTS, the corrected QT (QTc) interval may be normal on the 12-lead ECG.[1] In such cases, a more in-depth analysis is required, including genetic analysis. Beta-blockers and insertion of an implantable cardioverter defibrillator (ICD) in high-risk cases remain the cornerstone of management. Patients with LQTS can sometimes present with ventricular fibrillation (VF) storm and require emergency measures to treat the VF. Catheter ablation of culprit premature ventricular complexes (PVCs) responsible for triggering the VF episodes may be required in rare cases of electrical storm that do not respond to conventional measures, and this can be life-saving.[2,3]

To date, there have been very few reports on the use of catheter ablation in LQTS patients presenting with VF storm. We describe a case of emergency catheter ablation in a young woman with a normal QTc who presented with malignant VF storm that did not respond to conventional management. We discuss the diagnostic and management challenges involved in such cases, and the value of genetic testing in helping to refine the clinical diagnosis.

CASE REPORT

A 22-year-old woman presented to our institution for the first time with an out-of-hospital cardiac arrest, having suddenly collapsed at home with no apparent triggering events. Her partner was trained in cardiopulmonary resuscitation and managed to keep her alive until the arrival of the ambulance crew. The initial rhythm strip recorded by the paramedics showed VF, which was successfully defibrillated to sinus rhythm. She had no prior cardiac history and her only medical history was acne, for which she had been taking oral isotretinoin 20 mg daily for 12 months. She denied any illicit drug abuse. Her maternal grandfather and uncle had died suddenly at the ages of 41 and 23, respectively.

On arrival at the emergency department, the patient appeared to have fully recovered from the cardiac arrest. Her cardiovascular, respiratory and neurological examinations were unremarkable. Her initial 12-lead ECG (Fig. 1a) showed sinus rhythm with normal ventricular repolarisation and a QTc interval of 420 ms. Blood electrolytes and toxicology screen were all normal. Echocardiography showed a structurally normal heart with normal ventricular size and function. However, a few hours after admission, she developed frequent unifocal PVCs, some of which subsequently triggered VF episodes that required immediate defibrillation (Fig. 1b). She was initially started on a beta-blocker and an intravenous amiodarone infusion in an attempt to control the VF episodes. Her QTc interval increased to 450 ms after starting intravenous amiodarone. She continued to experience further PVC-triggered sustained and nonsustained VF episodes, and required over 15 external defibrillations to restore sinus rhythm during her first 24 hours of admission. Changing intravenous amiodarone to lidocaine and attempts at overdrive ventricular pacing failed to suppress the initiating PVCs and further VF episodes.

Therefore, a decision was made to undertake emergency electrophysiology study and ablation in order to map and ablate the triggering PVCs. The PVCs that initiated the recurrent VF episodes had a superior axis and left bundle branch block morphology (Fig. 2a), suggesting that the origin was likely to be from the right ventricular (RV) apical or inferior region. Using 3D electroanatomical mapping (CARTO XP) with magnetic

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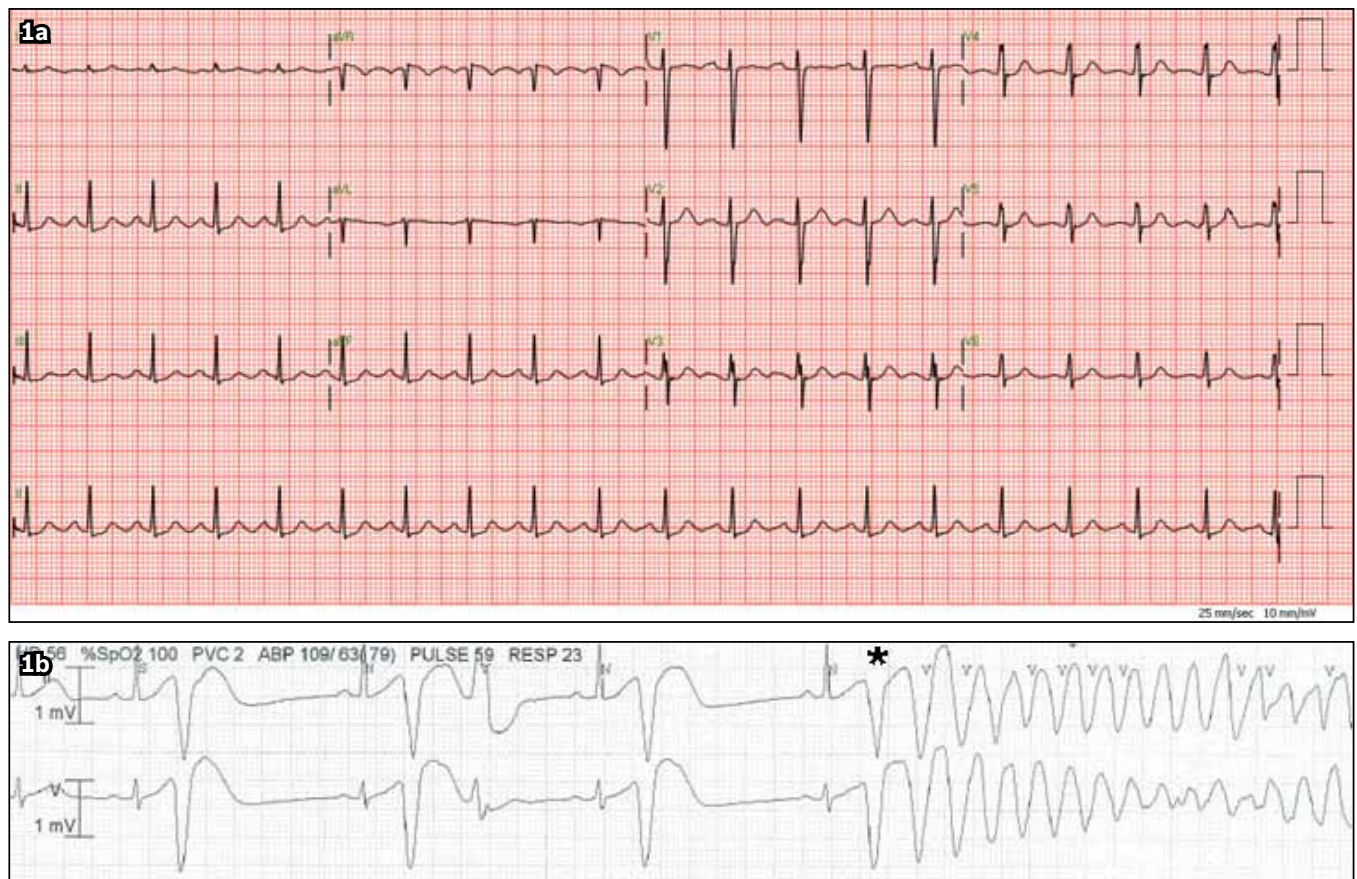
Fig. 1 (a) 12-lead ECG of the patient on admission after successful resuscitation shows the corrected QT interval measuring 420 ms. (b) Rhythm strip during continuous in-hospital monitoring shows run of ventricular bigeminy in which the 4th unifocal premature ventricular complexes (marked by *) triggered an episode of ventricular fibrillation that required direct current cardioversion.

navigation, the earliest activation site was identified to be at an RV inferoseptal location, 30 ms ahead of the PVC onset. Pace maps from the RV were used to narrow down the region of interest. All areas mapped in the left ventricle (LV) were later than the PVC onset, with poor pace maps. Ablation lesions were thus delivered at the earliest RV sites, with a radiofrequency (RF) energy of up to 40 W, with 50°C used for each lesion. Fluoroscopic and 3D electroanatomical images at the site of the earliest PVC activation are shown in Figs. 2b and 2c, respectively.

The initial RF lesion increased ventricular ectopy and resulted in VF, which required external cardioversion. Further episodes of VF that required cardioversion occurred during subsequent lesion deliveries (each preceded by the clinical PVC). Multiple RF lesions at the same site eventually decreased the frequency of the PVCs dramatically and increased the coupling interval from 260 ms to 290 ms. Right ventriculography performed at the same setting showed normal right ventricular function and subsequent cardiac magnetic resonance imaging showed normal myocardial structure and function, with no evidence of myocardial scar or arrhythmogenic right ventricular cardiomyopathy. The patient made a complete recovery over the next few days and had no further PVCs or VF episodes after returning to the ward. A dual-chamber ICD was inserted prior to discharge and she remained on an oral beta-blocker.

The patient was readmitted five months later after experiencing a single ICD defibrillation. Device interrogation and

examination of the stored intracardiac electrograms confirmed that she had experienced another episode of VF, which was triggered by a unifocal PVC. As we did not have a 12-lead ECG of this PVC, it could not be confirmed whether this was the same morphology as the triggering PVCs that were previously ablated. Her dose of beta-blocker was increased, and we decided to pace her heart (70 beats per minute) through the atrial lead of her ICD in order to shorten her QT interval and lower the chances of further VF episodes. She has remained well since, with no further PVCs or VF episodes at follow-up six months later. Subsequent genetic analyses revealed that the patient had a heterozygous c.2771G>A(p.Gly924Glu) nucleotide change in the *KCNH2* gene. There were no mutations in her *KCNQ1* and *SCN5A* genes. Therefore, it is likely that our patient had 'silent', previously undiagnosed LQTS type 2 and presented for the first time with an out-of-hospital VF arrest.

DISCUSSION
This case highlights a number of important and interesting points. Firstly, patients presenting with apparent 'idiopathic VF' may in fact have an underlying, previously undiagnosed cardiac ion-channelopathy, even though the initial 12-lead ECG may appear relatively normal. Secondly, genetic testing of patients with idiopathic VF may yield useful information that may have important implications for the patient or the patient's relatives. Finally, catheter ablation of PVCs that trigger recurrent VF
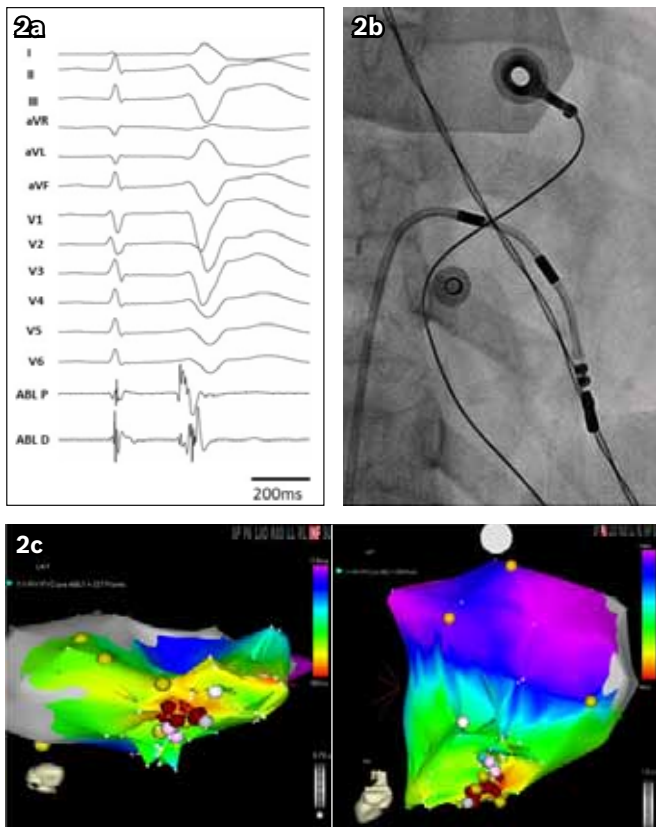
Fig. 2 (a) 12-lead surface ECG and ablation signals (Abl P and Abl D) at the site of origin of the triggering PVCs (30 ms prior to PVC onset). (b) Fluoroscopic image (right anterior oblique view) of stereotaxis ablation catheter at the successful ablation site. (c) 3D electroanatomical activation map of the right ventricle (inferior and posteroanterior views) shows the ablation points (brown circles) at the site of the earliest activation. The yellow circles represent sites of pace-mapping with poor correlation to the clinical PVCs, while the white circles represent the pace-mapping sites with good correlation (11/12 or 12/12 match). The colour scale on the right of the image represents how close the points in the map are to the point of earliest activation (closest points are in red, whilst the points furthest away are in blue/purple).

episodes may be necessary and life-saving in refractory cases that do not respond to conventional management of VF storm.

It is well recognised that approximately 25% of LQTS patients have a normal QTc[1] and that QTc durations in the range of 410–470ms may be observed among both LQTS carriers and noncarriers.[4] Genotype-confirmed patients with silent LQTS are at significant risk of sudden cardiac death compared to unaffected family members.[1] Thus, the finding of a normal QTc in our patient at presentation was clearly not sufficient to exclude a diagnosis of an inherited arrhythmogenic condition, although it was also possible that she had idiopathic VF. Subsequent results of genetic testing with the discovery of a heterozygous change in the c.2771G>A(p.Gly924Glu) nucleotide of the KCNH2 gene greatly helped to refine our diagnosis. This missense mutation of the C-terminal region, which results in a change in a moderately conserved amino acid from glycine to glutamic acid, has previously been described in one patient in the FAMILION® LQTS cohort.[5] Mutations in the KCNH2 pore-loop region have been known for some time to be associated with a significantly higher risk of cardiac events as compared to mutations found in other

regions of the channel,[6] although recent evidence suggests that this may not be true for women, who appear to have an increased risk of cardiac events regardless of the location of the KCNH2 mutation.[7] Furthermore, among LQTS type 2 patients, there are mutation-related differences in trigger-specific events and response to beta-blocker therapy. Pore-loop mutations are associated with arousal-triggered events, and patients with arousal-triggered events are more likely to respond to beta-blockers[8] This may partly explain why our patient (who did not have a pore-loop mutation or arousal-triggered events) did not respond well to beta-blockade, and required catheter ablation and subsequent atrial pacing to stabilise her condition.

The presentation of our patient at the age of 22 years, with an out-of-hospital VF arrest and subsequent VF storm triggered by unifocal PVCs, is quite unusual and differs from patients with congenital LQTS, who more commonly present with torsade de pointes and recurrent syncope, or are found to have QT prolongation on their 12-lead ECG upon screening if they have a family member with LQTS. It is unknown why our patient developed unifocal PVCs or why they occurred at the RV location. Another interesting possibility may be related to our patient having been on isotretinoin for 12 months prior to her admission. Isotretinoin has been reported to be associated with a number of adverse cardiac reactions (tachycardia and palpitations), although a recent study of 45 patients did not show any QT prolongation with isotretinoin.[9] In either case, the fact that the PVCs were unifocal enabled us to perform an electrophysiology study to map and ablate the source of the triggering PVCs. We cannot be certain of the relevance of the heterozygous KCNH2 gene mutation discovered in our patient, since the PVCs themselves could be responsible for the VF episodes. However, we believe that the combination of an underlying genetic abnormality and an external insult (e.g. infection or medication) may have been responsible for our patient's presentation.

Conventional management of patients presenting acutely with electrical storm involves the use of antiarrhythmic medication, treatment of potentially reversible causes (e.g. cardiac ischaemia in patients with acute coronary syndromes, electrolyte imbalances) and attempts to prevent recurrences.[10] In our patient, the cause of the electrical storm was not known when she first presented, as her QTc was normal. Hence, intravenous amiodarone was initially used when she had recurrent episodes of VF. This was changed to intravenous lidocaine when she continued to experience VF storm despite being on amiodarone.

The use of emergency catheter ablation of culprit PVCs that trigger VF episodes in electrical storm is sometimes required in rare refractory cases that do not respond to conventional measures.[2,3] However, there have been very few reports to date on the use of catheter ablation for VF storm in LQTS patients. Srivathsan et al described a case of successful catheter ablation in a patient with possible LQTS and VF, and emphasised the importance of precise electrophysiologic localisation.[11] In a case series of four patients with LQTS and VF, catheter ablation was

successfully used to treat recurrent VF episodes with no further episodes of VF, syncope or sudden cardiac death over a mean follow-up of 24 months.[12] The triggering PVCs in this series occurred in the RV outflow tract in one of the patients and in the distal Purkinje fibres in the other three. In our patient, the finding that the triggering PVCs arose from the ventricular myocardium rather than Purkinje system (there were no preceding Purkinje potentials seen at the successful ablation site), as well as the apical-septal location, are unusual and interesting features. Previous series of PVCs triggering VF arising from the right ventricle have reported more anterior sites in the RV outflow tract or His-Purkinje system.[13]

Our patient had a recurrence of VF five months post-ablation, which required an additional ICD defibrillation. This highlights the point that ablation of PVC triggers is not curative and not a substitute for ICD insertion in high-risk cases such as our patient. In a case series of catheter ablation in patients with idiopathic VF, the reported success rate was 82% at 63 months follow-up, with recurrence of VF at a median of four months.[14] Another case series reported a success rate of 89% at 24 months.[2] It was not reported whether these patients diagnosed with idiopathic VF had subsequent genetic testing for cardiac ion channelopathies or inherited arrhythmogenic diseases. Reithman et al recently reported the case of a 45-year-old woman who had an ICD inserted five years previously for VF, but she was subsequently diagnosed with LQTS type 3 (with a heterozygous missense mutation in the SCN5A-gene) only after she re-presented with recurrent torsade de pointes and the ECG showed prolonged QTc.[15] Our case underscores that patients with VF storm and a normal QTc may nonetheless have an underlying cardiac ion channelopathy, for which catheter ablation and antiarrhythmic medication may be useful, but not curative. Therefore, an ICD is also required. The other interesting aspect of our case is that some patients who appear to have idiopathic VF may in fact have an underlying channelopathy, which may be missed if genetic testing is not performed. This requires a higher index of suspicion, especially in younger patients with recurrent VF without any discernable cause and a strong family history of sudden cardiac death. A correct and accurate diagnosis has important implications both to the patient and to the patient's immediate family. However, the results of genetic testing may not be conclusive or cost-effective, and thus the decision to perform such tests needs to be carefully discussed with the patient.

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