

Sudden cardiac arrest in a patient with malignant mitral valve prolapse with CACNB2 gene mutation: a simple coincidence or coexistence? —a case report

Nirmalatiban Parthiban ^{1*} and Huzairi Sani^{2,3,4}

¹Department of Internal Medicine, Hospital Selayang, Batu Caves, Selangor 44000, Malaysia; ²Cardiology Unit, Department of Internal Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor 47000, Malaysia; ³Integrative Pharmacogenomics Institute (iPROMISE) UiTM Puncak Alam, Puncak Alam 42300, Selangor, Malaysia; and ⁴Cardiac Vascular and Lungs Research Institute (CaVaLRI), Pusat Perubatan Universiti Teknologi MARA, Sungai Buloh campus, Sungai Buloh 47000, Selangor, Malaysia

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Background

Despite recent advances in cardiology, sudden cardiac death remains to be a significant challenge, and the precise cause for a large proportion of sudden cardiac arrests remains unclear.

Case summary

A 48-year-old fit and healthy medical personnel with no previous medical illness suffered from ventricular fibrillation at his work-place and was successfully resuscitated. Although the basal electrocardiogram did not show a Brugada pattern, we identified mutations in the CACNB2 genes (Chr10: 18150879 and Chr10: 18539538 variants), which are pathogenic variants linked to the Brugada syndrome. A transthoracic echocardiogram and cardiac magnetic resonance revealed mitral valve prolapse (MVP) with characteristics of Barlow's disease, as well as malignant MVP features such as the presence of bileaflet prolapse, mitral annular disjunction, and inferior and inferolateral left ventricular wall fibrosis.

Discussion

To the best of our knowledge, this is the first case report on sudden cardiac arrest in a patient with malignant MVP with a CACNB2 gene mutation. This study highlights the merit for further research to establish standardized criteria for the diagnosis of malignant MVP, for the primary prevention of sudden cardiac death. Cardiac MR should also be part of the diagnostic evaluation of MVP to allow for the early detection of arrhythmogenic features, especially left ventricular fibrosis. We also suggest that the utility of genetic testing should be complementary to the current diagnostic tools for unexplained cardiac arrest and patients with MVP. This would help to better understand the genetic basis between these two conditions for better risk stratification and early cardiac intervention.

Keywords

Sudden cardiac death • Mitral valve prolapse • CACNB2 mutation • Case report

ESC Curriculum

5.6 Ventricular arrhythmia • 5.10 Implantable cardioverter defibrillators • 8.5 Primary prevention • 9.7 Adult congenital heart disease • 8.6 Secondary prevention

* Corresponding author. Email: nirmalatibanparthiban@gmail.com

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Learning points

- This study highlights the need for further research to establish standardized diagnostic criteria for malignant mitral valve prolapse.
- Mitral valve prolapse should not be disregarded as a benign condition, and physicians should recognize the features of malignant mitral valve prolapse and should include cardiac MR as part of their evaluation.
- The utility of genetic testing should be complementary to the current diagnostic tools for unexplained cardiac arrest and patients with mitral valve prolapse. This would help to better understand the genetic basis between these two conditions for better risk stratification and early cardiac intervention.

Introduction

Cardiovascular diseases are responsible for ~17 million deaths every year on a global scale, about a quarter of which are sudden cardiac deaths (SCDs).¹ Sudden cardiac death is an unexpected natural death resulting from a cardiac cause within a short duration. Some of the important causes of SCD include ischaemic heart disease, structural cardiac abnormalities, cardiomyopathies, and electrophysiology disorders. Despite recent advances in cardiology, sudden cardiac arrest (SCA) has been a significant challenge, and a large proportion of non-coronary cardiac arrest cases remain unclear.

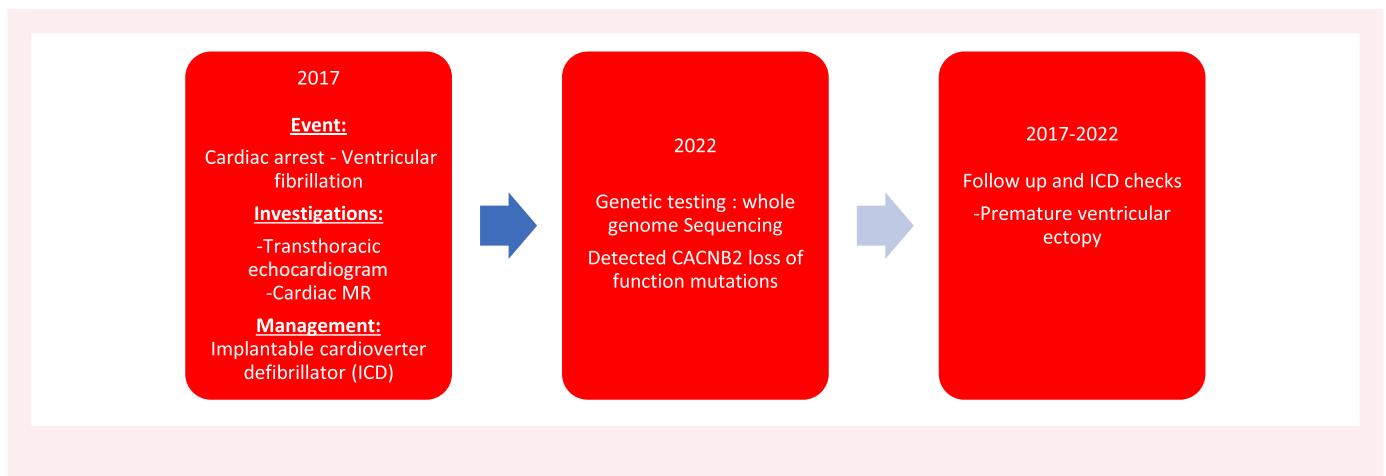
Based on the POST-SCD study, the rate of sudden arrhythmic death (SAD) amongst all sudden causes of death was highest amongst Asians, with a 3% of survival rate.² Amongst the common inherited arrhythmia syndromes is Brugada syndrome, one of the major causes of SCD in young patients. Brugada syndrome is a familial disease that displays an autosomal dominant mode of transmission. In the past two decades, several Brugada syndrome-associated genes were reported, most of which primarily encode sodium, potassium, and calcium channels. Amongst the pathogenic genetic variants associated with Brugada syndrome is CACNB2 gene mutation, a loss of function mutation in the

cardiac calcium channel, which is associated with 4–5% of Brugada syndrome cases.^{3,4}

One of the common cardiac structural defects being increasingly recognized for SCD is mitral valve prolapse (MVP), with an estimated prevalence of 2.4% in the general population. Although the incidence of MVP-related SCD was initially assumed to be trivial, recent observational data show that the estimated risk for SCD is over 2% amongst patients with MVP compared with the general population.^{5,6} Barlow's disease is the commonest cause of degenerative mitral valve disease after fibroelastic deficiency, and it is characterized by the prolapse of both leaflets with markedly thickened and diffusely redundant myxomatous tissue. Recent systemic reviews have reaffirmed the association of SCD with MVP.^{7,8} These studies reported features of malignant MVP (MVP-associated malignant ventricular arrhythmias), including inverted T wave in the lateral leads, ventricular ectopy on electrocardiogram (ECG), prolapse of both leaflets, mitral annular disjunction (MAD), and left ventricular fibrosis.

In this case report, we have recounted a rare experience of cardiac arrest due to ventricular fibrillation in a patient with malignant MVP, with a pathogenic genetic variant associated with Brugada syndrome.

Timeline



Case report

A 48-year-old fit and healthy medical personnel was in his typical state of health when he suddenly collapsed in his clinic. Resuscitation manoeuvres were performed by the mobile emergency medical unit, and they promptly recognized ventricular fibrillation. The patient was successfully resuscitated. He had no previous medical history nor any symptoms of angina, palpitation, fever, respiratory tract infection, or

syncopal/pre-syncopal attacks prior to the event. He has no previous history of SCD or young onset of cardiovascular disease in the family. He was not on any traditional supplements/medications. Cardiovascular examination revealed a pansystolic murmur best heard over the mitral area radiating to the axilla. Other clinical examinations were unremarkable. Blood investigations ruled out infective, acute ischaemic, and toxicological causes. Electrocardiogram post-resuscitation revealed premature ventricular contraction with no

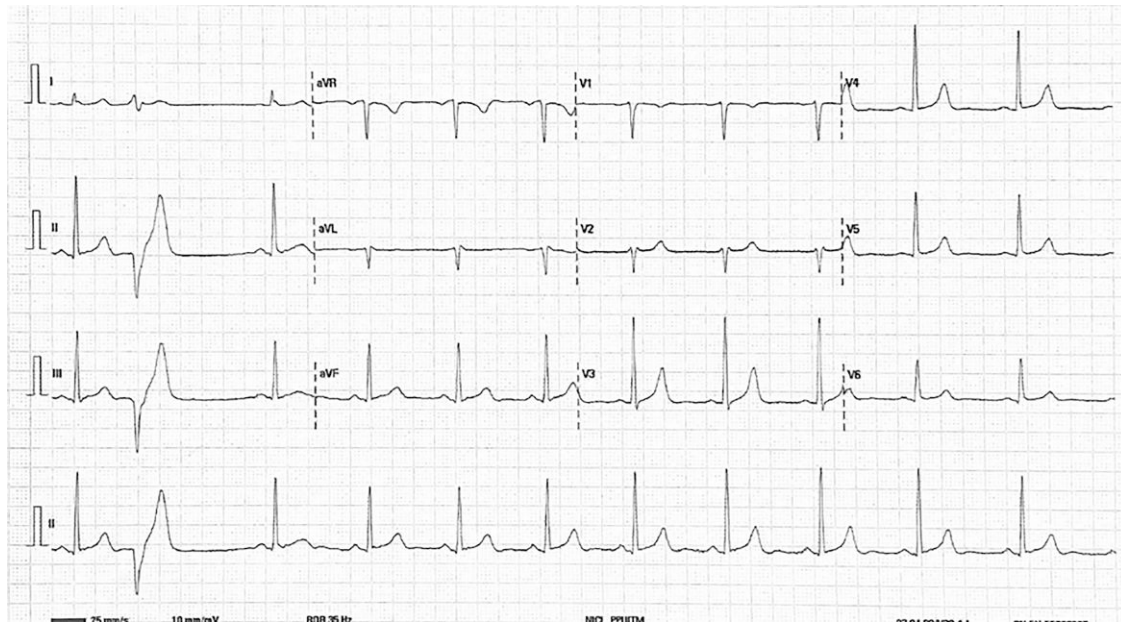


Figure 1 Electrocardiogram post-resuscitation showed premature ventricular contraction with no evidence of pseudo-right bundle branch block, prolonged QT, delta, or epsilon waves.

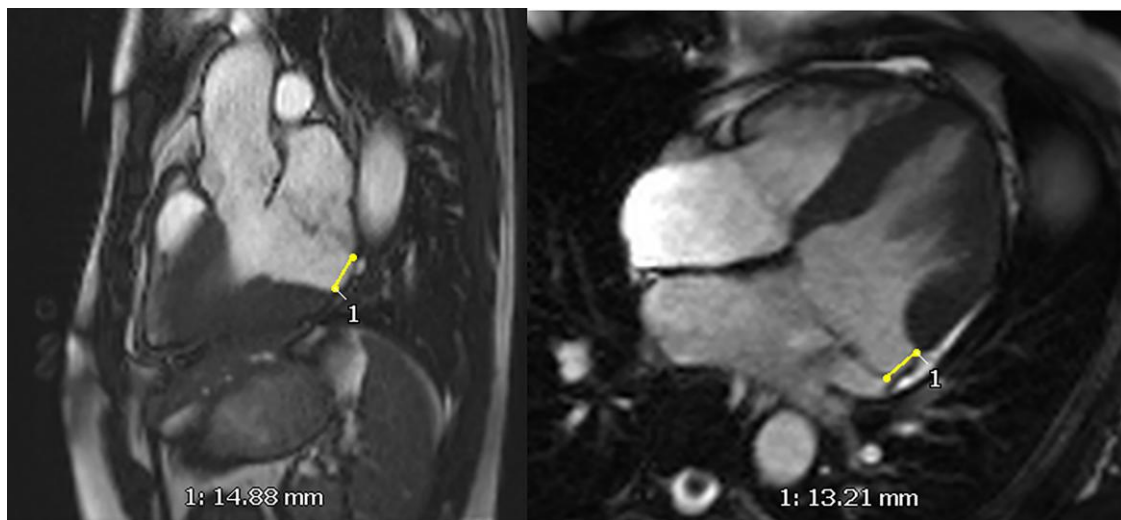


Figure 2 The double arrow shows mitral annular disjunction on cardiac magnetic resonance imaging.

evidence of pseudo-right bundle branch block, prolonged QT, delta, or epsilon waves (Figure 1).

A transthoracic echocardiogram and cardiac MR showed features of Barlow's disease. The transthoracic echocardiogram showed bileaflet MVP, a MAD measuring 1.2 cm, a moderate mitral regurgitation, a dilated mitral valve annulus measuring 4.5 cm, and a normal left ventricular size with normal systolic function with a left ventricular ejection fraction of 58%. There was no gross regional wall abnormality. The cardiac MR also showed MAD (Figure 2), thickened valves, bileaflet prolapse, and

dilated mitral valve annulus. The late gadolinium enhancement (Figure 3) revealed inferior and inferolateral ventricular wall fibrosis. There was no evidence of acute myocardial inflammation or oedema. Being a young patient with no previous medical illness, to obtain more information on this unexplained cardiac arrest, we performed whole genome sequencing and found mutations in the CACNB2 genes (Chr10: 18150879 and Chr10: 18539538 variants). Single coil electrode dual-chamber ICD implantation was offered as a secondary prevention, as subcutaneous ICD (S-ICD) was unavailable in our centre at the time (Figure 4).

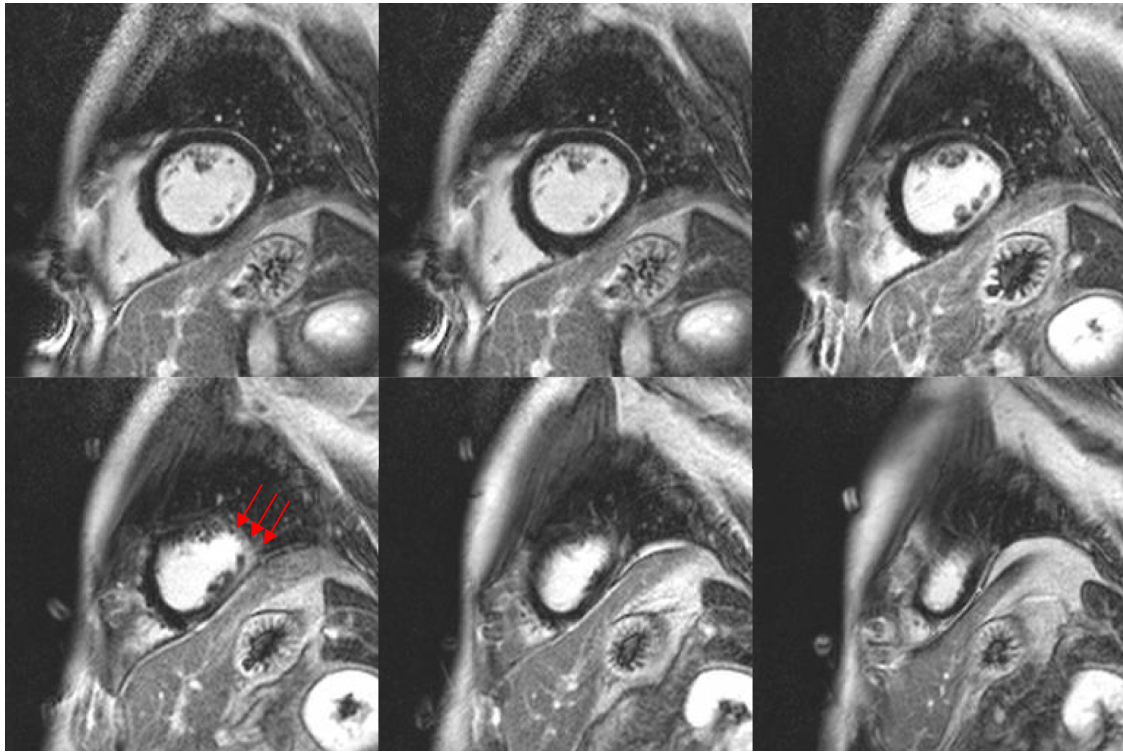


Figure 3 The arrows show late gadolinium enhancement on cardiac magnetic resonance imaging—revealing inferior and inferolateral ventricular wall fibrosis.

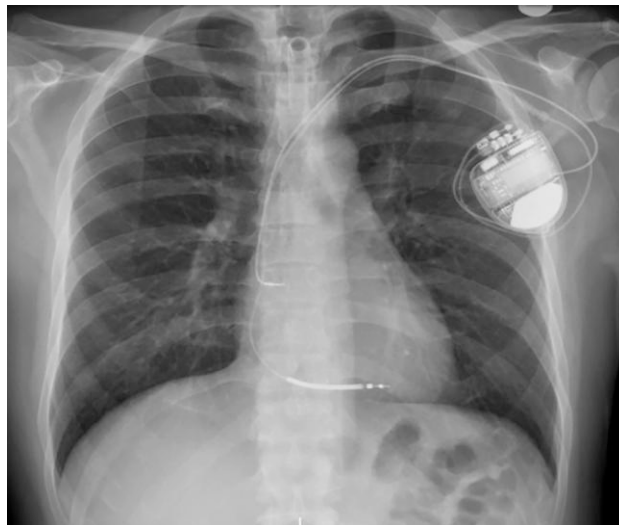


Figure 4 Single coil electrode dual-chamber implantable cardioverter defibrillator.

During the 6-monthly follow-ups, the ICD check showed only multiple frequent premature ventricular contractions. The work on offspring's genetic screening for mutations in CACNB2 genes after obtaining a written informed consent in the pre-test genetic counselling sessions is currently ongoing.

Discussion

Despite significant advances in cardiology, SCA has been a major challenge over the past few decades. Identification of the precise cause of SCD has major implications for better patient management.

In line with recent studies suggesting genetic evaluation for unexplained SCA, we performed whole genome sequencing that detected mutation in the CACNB2 genes.^{9,10} Mutations in the α 1-(CACNA1C), β 2-(CACNB2), and α 2 δ -(CACNA2D1) subunit genes of cardiac L-type channels account for 2–4% of patients with Brugada syndrome.¹¹ L-type calcium channel regulates action potential dome, and calcium channel dysfunction can thus result in abnormal action potential duration, leading to malignant arrhythmias. Although the genetic mutation is not part of the diagnostic criteria for Brugada syndrome, numerous studies have demonstrated the association between the loss of function mutation of the cardiac L-type calcium channel and the Brugada syndrome phenotype.^{12,13,14}

In recent years, the arrhythmogenic potential of MVP causing malignant arrhythmias has been increasingly recognized. Han *et al.*¹⁵ investigated autopsies of SCD and revealed that individuals with isolated MVP have significantly increased cardiac mass, mitral annulus size, and left ventricular fibrosis, and 94% of them had ventricular fibrillation. Features of malignant MVP witnessed in our patient include bileaflet prolapse, MAD, premature ventricular contraction, and inferior and inferolateral left ventricular wall fibrosis, which were also similar to the features described in a recent literature review by Lakshmi *et al.*⁸

The precise mechanism for MVP causing malignant arrhythmias remains unknown. The interactions of the mitral valve apparatus with local myocardium and MAD via traction may result in fibrosis and regional wall conduction disturbances. Therefore, cardiac MR would be an essential part of the evaluation and follow-up for MVP patients for the early detection of left ventricular fibrosis. Pathologically silent cardiac channelopathies are responsible for at least one-third of sudden unexplained deaths in the young (SUDY).¹⁶ A retrospective study showed that SUDY decedents with an isolated MVP were more likely to possess ≥ 1 American College of Medical Genetics (ACMG)—classified pathogenic/likely pathogenic variants.¹⁷ Genes responsible for SCD may be capable of causing maladaptive myocardial/electrical responses to the mechanical stress generated by genetically unrelated MVP. This theory is further supported by a recent case report by Mahajan *et al.*,¹⁸ which highlights the presence of pathogenic variants (LMNA-encoded lamina A/C and SCN5a-encoded Na1.5 channel) in a SCA patient with MVP. To date, the genetic basis of malignant MVP remains largely unexplored.

To the best of our knowledge, this is the first case report highlighting the presence of CACNB2 loss function mutation in a SCA survivor with malignant MVP. In our opinion, the genetic evaluation should complement other extensive investigations for SCA and also for patients with MVP. More studies, however, are needed to determine whether the genetic mutations are merely over-representation or simply arisen owing to chance. Nevertheless, we believe whole genome sequencing will not only assist in delivering targeted therapy and strategic follow-up but will also be helpful in future family screening. Next-generation sequencing of arrhythmogenic MVP pedigrees has the potential to identify novel arrhythmogenic MVP susceptibility genes to further enhance our understanding of the molecular mechanisms. As arrhythmogenic MVP causing SCA is no longer trivial, a greater understanding of the potential genetic basis of this disorder may help clinicians identify the small number of individuals with MVP who may benefit from antiarrhythmic

drugs, ICD implantation for primary prevention of SCD, or even early mitral valve reconstruction. Transvenous ICD was implanted in our patient, as S-ICD was unavailable in our centre at the time. Subcutaneous ICD can be a reliable therapeutic alternative, especially for young SCA patients, in the future.

Lead author biography



Dr. Nirmalatiban Parthiban received his medical degree from the Royal College of Surgeons in Ireland. He obtained the Membership of the Royal College of Physicians of Ireland (MRCPI) in 2022. He is currently working in the Department of Internal Medicine at Hospital Selayang, Malaysia. He has a special interest in cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports*.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that a written informed consent for the publication of this case report was obtained from the patient, in line with the Committee on Publication Ethics (COPE) guidelines.

Conflict of interest: None declared.

Funding: None declared.

Data availability

The data that support the findings of this study will be available from the authors upon reasonable request.

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