

# You cannot ablate the Lernaean Hydra: SCN5A mutation in a patient with multifocal ectopic Purkinje-related premature contractions syndrome treated with Flecainide and an implant of a subcutaneous defibrillator—a case report

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## Background

SCN5A mutations may present with different clinical phenotypes such as Brugada syndrome, long QT3 syndrome, sick sinus syndrome, atrial fibrillation, dilated cardiomyopathy, and the least known multifocal ectopic Purkinje-related premature contractions syndrome.

## Case summary

We report a case of a 29-year-old woman with palpitations due to multifocal premature ventricular complexes (PVCs) and a family history of sudden death. The previous electrophysiological study had shown that PVCs arose from Purkinje fibres but catheter ablation was unsuccessful. Cardiac magnetic resonance (CMR) imaging demonstrated non-ischaemic areas of subendocardial fibrosis at multiple left ventricular (LV) segments with concomitant dilatation and mild systolic impairment. Amiodarone suppressed the ectopy but caused hyperthyroidism. Due to recent pregnancy, she received no antiarrhythmics which resulted in PVC burden increase and further deterioration of the ejection fraction (EF). After gestation, amiodarone was reinitiated and switched to flecainide after implantation of a subcutaneous defibrillator as a safety net. At follow-up, LV function had almost normalized. Genetic analysis confirmed an SCN5A mutation.

## Discussion

Multifocal ectopic Purkinje-related premature contractions syndrome is associated with SCN5A mutation which in our case (R222Q) is the most common described. Flecainide can be an appropriate treatment option when ablation is ineffective. Defibrillator—even a subcutaneous type—could be implanted in cases of LV dysfunction or scar. PVCs suppression by flecainide and restoration of EF implies an arrhythmia-induced mechanism of LV impairment.

## Keywords

MEPPC syndrome • SCN5A • Subcutaneous defibrillator • Flecainide • Case report

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## Learning points

- The presence of a chaotic electrocardiogram in terms of multifocal premature ventricular complexes in a young patient raises the suspicion of Multifocal Ectopic Purkinje-related Premature Contractions syndrome and SCN5A mutation analysis supports the diagnosis.
- Flecainide—with the back-up of a subcutaneous ICD in an individualized approach—is an alternative option as it is more available and less toxic compared to hydroxyquinidine and amiodarone, respectively.
- Radiofrequency ablation is not suggested due to the multiple foci of premature beats consistent with the nature of the disease.

## Introduction

Gene mutations account for various arrhythmic disorders that are associated with sudden cardiac death.<sup>1</sup> SCN5A is a member of a family of voltage-gated sodium ion channels<sup>2</sup> and plays a key role during the rapid upstroke of the action potential and thus mediates the myocyte depolarization by allowing a rapid influx of sodium ions.<sup>3</sup>

Gain or loss of function SCN5A mutations is associated with LQT3 or Brugada syndrome, respectively.<sup>4</sup> However, a less known phenotype is related to gain of function mutation at the SCN5A gene. Its clinical manifestation consists of multifocal ectopic ventricular beats with narrow QRS width, indicating a Purkinje fibre origin. This Multifocal Ectopic Purkinje-related Premature Contractions (MEPPC) syndrome was first presented with this term by Laurent et al.<sup>5</sup> Till then, there were few references in the literature about families with similar characteristics. The R222Q SCN5A mutation accounts for most of the cases.<sup>5–9</sup>

## Timeline

2012	Palpitations. Electrocardiogram demonstrates multiple premature ventricular beats (PVCs)
2013	Sister died suddenly. No autopsy done. Unknown medical history
2013	Electrophysiology (EP) study—ablation. PVCs mapped at the left ventricle (LV) preceded by a purkinje potential
2013	Amiodarone was started as PVCs persisted post ablation but treatment lasted for 1 year as she developed hyperthyroidism
2014	Cardiac magnetic resonance (CMR) imaging revealed areas with subendocardial fibrosis
2017	Referred to our clinic. More than 30 000 PVCs/24 h on b-blocker
2019 January	Pregnant. Stopped any antiarrhythmic
2019 May	Genetic test: SCN5A mutation
2019 September	Post-partum severe LV impairment (ejection fraction 20%)
2019 November	Subcutaneous defibrillator (S-ICD) implanted.
	Flecainide started after a short course on Amiodarone at the post-partum period
2020 March	Still on flecainide.
	Substantial decrease in PVC burden and LV function improvement

## Case presentation

A 29-year-old patient was referred to the outpatient clinic 3 years ago due to palpitations and a high burden of premature ventricular contractions (PVCs) in order to evaluate the need of a redo procedure as a previous failed ablation was performed 7 years ago. No history of syncope or presyncope was evident, but a family history of

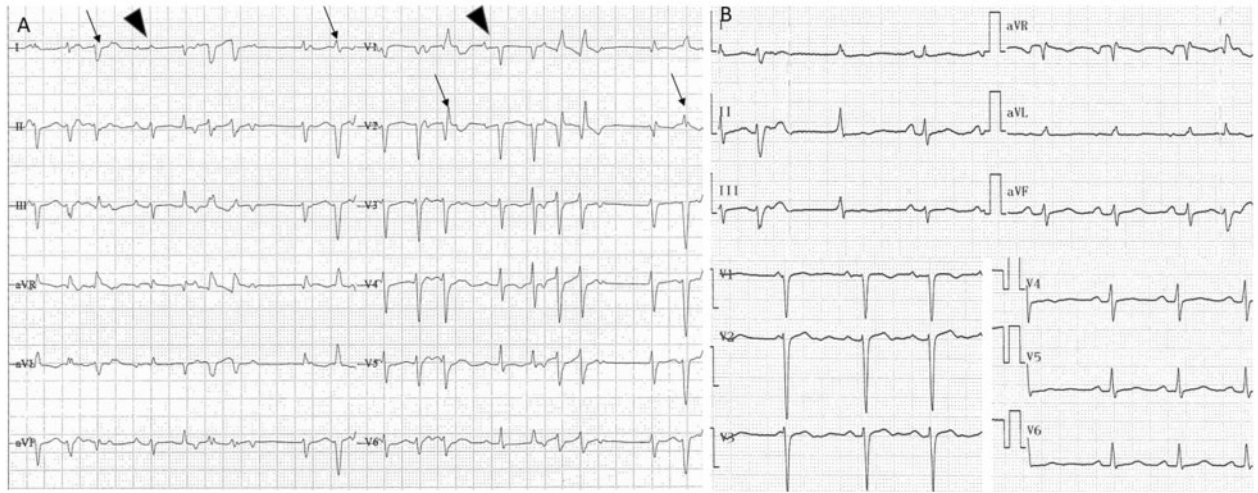
sudden cardiac death (SCD) was present. Her sister died suddenly at the age of 18 but an autopsy was not performed, and her mother had a defibrillator (ICD) implanted due to unclassified cardiomyopathy. Further clinical information was not provided. Physical examination was unremarkable except for the presence of irregular heart rate. Electrolytes, thyroid functions, and brain natriuretic peptide were within normal ranges.

At the time of this first visit, the patient was already on a beta-blocker and an electrocardiogram (ECG) showed multifocal PVCs in a repetitive pattern with narrow QRS width, while sinus beats were rare (Figure 1A).

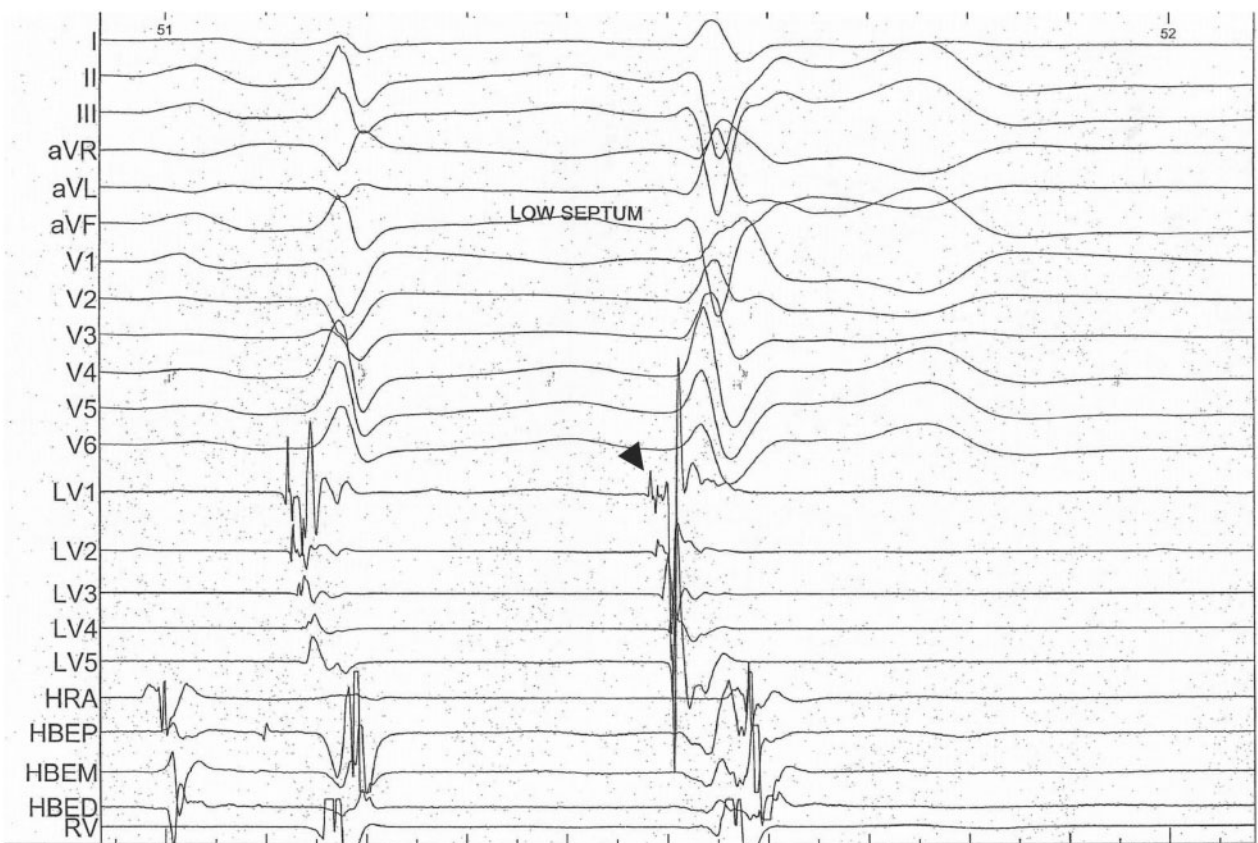
Echocardiogram showed mild left ventricular (LV) dysfunction and ambulatory 24 h Holter recorded more than 30 000 PVCs.

The patient had already an EP study 7 years ago. A dominant PVC morphology was mapped, and the source of origin was located at the inferoseptal LV segment preceded by a discrete Purkinje potential (Figure 2). Radiofrequency (RF) lesions were applied, and the acute result was deemed successful. When PVCs recurred post-ablation, amiodarone was commenced but was stopped 1 year later due to hyperthyroidism.

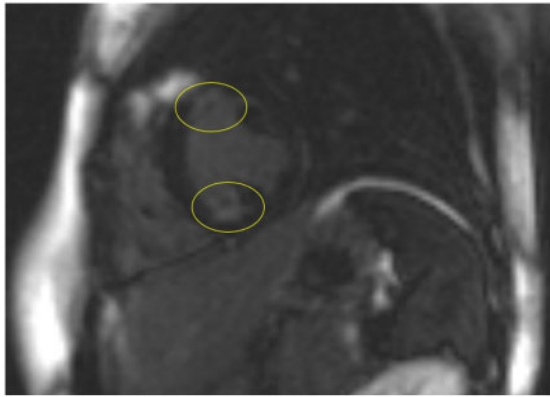
Cardiac magnetic resonance (CMR) with gadolinium enhancement demonstrated subendocardial fibrotic areas and a mild increase in the end-diastolic and systolic LV dimension with preserved ejection fraction EF (Figure 3). Inferoseptal LV scar due to RF lesions, albeit in adjacent region, cannot be excluded. Notably, an antero-septal LV scar is unrelated to the previous ablation procedure.



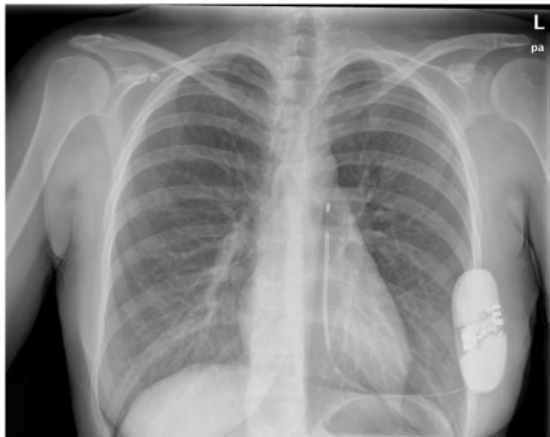
**Figure 1** Electrocardiogram of the patient (A) at baseline showing multifocal premature ventricular complexes in a repetitive pattern with narrow QRS width (arrows), while sinus beats were rare (arrowheads) and (B) post-flecainide treatment showing clear sinus rhythm.



**Figure 2** Electrophysiology study exhibited a dominant premature ventricular complex morphology arising from the inferoseptal left ventricular segment preceded by a discrete Purkinje potential (arrowhead).



**Figure 3** Cardiac magnetic resonance with gadolinium enhancement demonstrated subendocardial fibrotic areas (yellow circles).



**Figure 4** Chest X-ray after implantation of a subcutaneous ICD.

The ECG characteristics, the presence of Purkinje potential at the site of earliest activation and the family history of SCD—despite the lack of extra clinical information—raised the suspicion of MEPPC syndrome. Genetic testing of the whole family members was recommended, but only the patient proceeded. She was discouraged from a redo ablation considering the high likelihood of failure.

The patient had been lost from follow-up the following 2 years till her pregnancy when she decided to proceed to genetic testing. It was found that she had a gain of function mutation at the exon 6 of the SCN5A gene—c.665G>A (p.Arg222Gln, R222Q). Thus, the clinical diagnosis of MEPPC syndrome was further supported.

During pregnancy, beta-blocker treatment was terminated for foetus safety. At the 36th week of her gestation she presented with dyspnoea, PVC burden was further increased, and EF was estimated at 20%. As amiodarone was contraindicated in pregnancy on the advice of the obstetric team, it was decided that labour would be induced, as having been discussed at a multidisciplinary meeting. There were

no significant health consequences to the neonate. Amiodarone was commenced in the puerperium due to depressed EF (20%) and the patient was advised against breastfeeding. Due to its previous toxic effect, amiodarone was given on a short-term basis. The patient passed the necessary pre-implant screening test and subsequently a S-ICD was implanted (Figure 4). Having the ICD as a safety net, amiodarone was replaced by flecainide despite the ongoing LV dysfunction and the presence of scar. At her last follow-up, 4 months after flecainide initiation, ECG showed clear sinus activity (Figure 1B), PVCs were reduced to 5000/24 h, EF was gradually improved to almost normal (EF 50%) and flecainide was well tolerated.

## Discussion

SCN5A mutations are detected in 1.7% of dilated cardiomyopathy (DCM) families and, in particular, R222Q mutation was associated with PVCs—as in our patient.<sup>10</sup> Our patient's SCN5A mutation (p.Arg222Gln, R222Q) is the most common described one in the literature.<sup>5–9</sup> Other SCN5A mutations are also reported causing the same clinical manifestation.<sup>11–13</sup>

Gain of function SCN5A mutation results in altering the gating properties of Na<sub>v</sub>1.5 (sodium channel subunit). Consequently, a small percentage of sodium channels are inactivated at more depolarized potentials causing increase of the window current. This leads to the onset of premature action potentials during the repolarization phase of the Purkinje cells.<sup>14</sup>

The suspicion of the MEPPC should be raised by the presence of polymorphic ventricular ectopic beats with relatively narrow QRS indicating a septal origin, such as the Purkinje fibres irrespective of exercise. Such an ECG manifestation is met in posterior papillary muscle PVCs, but our working diagnosis is enhanced by concomitant positive family history of sudden cardiac death and SCN5A mutation. Notably, PVCs in idiopathic ventricular tachycardia (VT) are monomorphic and usually originate from the outflow tract. Bundle branch re-entrant tachycardia is excluded due to its typical left bundle branch block (LBBB) QRS pattern presented with haemodynamic instability.<sup>15</sup>

Left ventricular dysfunction was timely correlated with the recurrence of PVCs, secondary to beta-blocker cessation during pregnancy. This indicates an arrhythmia mediated mechanism and is further supported by the restoration of ventricular function upon flecainide initiation and a decrease in PVC burden. However, it is unclear at what extent pregnancy-related hormonal changes or increased sympathetic tone contribute to left ventricular dysfunction and PVC burden.

Treatment of PVCs is essential in case of high burden and concomitant LV dysfunction as the latter is regarded arrhythmia mediated.<sup>16</sup> Drugs in MEPPC syndrome are more effective than ablation due to the diffuse origin of the PVCs.<sup>13</sup> Hydroxyquinidine—which is further reported in the literature<sup>5,9,13</sup>—is not available in our country. Laurent *et al.*<sup>5</sup> describe a family with MEPPC syndrome that flecainide reduced ectopy in most of the affected members. Since then, flecainide has been used in other cases with good response<sup>8,12</sup> as well as amiodarone.<sup>6,11</sup> Given the LV dysfunction, amiodarone was the least proarrhythmic option in the post-partum period in our patient. Due to the previous history of amiodarone-induced hyperthyroidism,

amiodarone was used only for a short period and was switched to flecainide when an ICD had already been implanted.

Flecainide treatment resulted in improvement of symptoms and LV function due to elimination of PVCs which confirms that previous LV impairment was arrhythmia-induced. Upon initiation of flecainide treatment, LV function was still impaired, rendering flecainide potentially proarrhythmic given the presence of scar as well. Left ventricular fibrosis in MEPPC syndrome is a rare finding but its presence should not exclude the diagnosis.<sup>13</sup> Despite the lack of syncope, the patient was in high arrhythmic risk due to LV dysfunction and fibrosis and an S-ICD was implanted. There was no indication for (i) bradycardia pacing, (ii) cardiac resynchronization, and (iii) antitachycardia pacing. Therefore, S-ICD was preferred to a conventional transvenous defibrillator that would expose our young patient to long-term risk of infection. To our knowledge, it is the first time that an S-ICD has been implanted in MEPPC syndrome.

## Conclusion

Specific ECG characteristics factors should raise the suspicion of MEPPC syndrome in a young patient and possible SCN5A mutation should be sought. Flecainide is a reasonable treatment choice and a subcutaneous defibrillator could be recommended under certain circumstances. Ablation seems to be ineffective as there are multiple targets—a contemporary Lernaean Hydra in Electrophysiology.

## Lead author biography



Dr Georgios Leventopoulos is a Consultant in Electrophysiology at the University Hospital of Patras, Greece since 2017. His training in Electrophysiology took place in UK between the years 2012-2016 when he had been working as a fellow in Royal Brompton Hospital, London, and University Hospital of Southampton. He had been awarded the step2 EHRA accreditation both in Electrophysiology and Implantable

Devices. Research Interests: Atrial fibrillation, Arrhythmias in Congenital heart disease, Devices programming, and Channelopathies.

## Supplementary material

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

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

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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