Multifocal ectopic premature Purkinje-related complexes syndrome in children

Ming-Lon Young, MD, MPH, FHRS, CCDS,* Orhan Kilinc, MD, CCDS, CEPS-P,* Daniel Benhayon, MD†

*From the *Joe DiMaggio Children's Hospital, Hollywood, Florida, and †Memorial Health System, Hollywood, Florida.*

Introduction

Multifocal ectopic premature Purkinje-related complexes syndrome (MEPPC) is a rare form of arrhythmia involving the entire His-Purkinje system (HPS), characterized by frequent polymorphic premature ventricular contractions (PVCs) with relatively narrow QRS, and is associated with a high probability of dilated cardiomyopathy.[1–3] MEPPC can manifest in children, even in the fetal stage. In this case series, we report 5 pediatric MEPPC patients with ages ranging from newborn to adolescent and severity ranging from asymptomatic to presentation with ventricular tachycardia (VT) storms.

Case report

Table 1 presents a summary of the demographic data, clinical findings, and treatment of the 5 patients, who came from 3 unrelated families.

Case 1

A 16-year-old patient presented to the emergency room with palpitations and shortness of breath. The electrocardiogram (ECG) showed incessant, relatively narrow QRS VT (170–200 beats/min) with right bundle branch block (RBBB) morphology and superior axis. He had decreased cardiac systolic function. After intubation, he was in a bigeminal pattern with 2 dominant morphologies: a left bundle branch block, inferior axis; and RBBB, superior axis.

Review of his newborn records revealed an asymptomatic nonsustained narrow QRS tachycardia with ventriculoatrial dissociation.

Cardiac magnetic resonance imaging showed a markedly enlarged left ventricle (LV) with severely decreased function (ejection fraction [EF] 18%), diffuse fibrosis, and late gadolinium enhancement in the LV free wall. Since he presented with both VT and low LV EF, and never had a long enough period of good control of his VT to allow LV function recovery, it was unclear whether he had a primary cardiomyopathy or not.

In the following 8 months he had 4 electrophysiologic studies (EPS).

In EPS_1, he was in nonsustained VT (Figure 1, left panel) and the ectopies were originating over the entire HPS: left posterior fascicle, left posterior papillary muscle, left anterolateral fascicle, and right proximal His bundle (HB). All these (preceded by either Purkinje fibers or ventricular breakout

KEY TEACHING POINTS

- Multifocal ectopic premature Purkinje-related complexes (MEPPC) are characterized by frequent polymorphic premature ventricular contractions (PVCs) of short coupling interval, sharp initial QRS deflection, relatively narrow QRS duration (Purkinje system hyperexcitability), and a family history, and is associated with dilated cardiomyopathy. MEPPC should be considered in young patients with frequent multifocal PVCs with relatively narrow QRS.
- Mutations in *SCN5A* genes were shown to be associated with MEPPC. However, presence of an *SCN5A* variant is not required for the diagnosis.
- In the literature, quinidine, hydroquinidine, amiodarone, and flecainide all have been reported as treating the PVCs with success. Ivabradine, a relatively new drug, can be useful in some MEPPC patients.
- In severe cases with ventricular tachycardias, extensive catheter ablations may be required to achieve freedom from arrhythmias. Owing to the proximity of lesions to the His bundle, ablation-induced heart block may be inevitable. Therefore, medications should first be tried for rhythm control, which may result in normalization of the LV function in at least some patients.

KEYWORDS Multifocal ectopic premature Purkinje-related complexes syndrome; *SCN5A* gene mutation; His-Purkinje system; Catheter ablation; Children

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Address reprint requests and correspondence: Dr Ming-Lon Young, Joe DiMaggio Children's Hospital, 1150 North 35 Ave, Suite 490, Hollywood, FL 33021. E-mail address: mingyoungMDEP@gmail.com.

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Table 1 Summary of the demographic data, clinical findings, and treatment of patients in the 5 cases

Case	Age (years) at Diagnosis	Age (years) at Last seen / death	Sex	Phenotype	Other diagnosis	Medications Ineffective	Medications Effective	Ablation	Genotype	Follow-up	Comment
1	14	17	M	Multiform incessant VT, atrial flutter, CM	–	BB, CCB, mexiletine, flecainide, amiodarone	None	Failed (4)	*SCN5A* p.Arg814Trp -c.2440 C>T	Sustained VF on VAD; died of VAD complication	De novo mutation
2	15	17	F	Multiform nonsustained VT	–	BB, ivabradine	Flecainide	None	*SCN5A* p.Arg222G - c.665 G>A	Rare PVC	Sister of case 3 patient
3	13	14	M	Multiform nonsustained VT	–	BB	Flecainide	None	*SCN5A* p.Arg222G - c.665 G>A	Rare PVC	Brother of case 2 patient
4	15	25	F	Multiform incessant VT	Polyglandular autoimmune syndrome (type 3)	BB, CCB, flecainide, mexiletine, quinidine, amiodarone	None	Success after 7 ablations	Negative	No ventricular ectopy; normal cardiac function	Mother of case 5 patient
5	1 day	2	M	Multiform nonsustained JT	Double-inlet left ventricle	BB	Ivabradine	None	Negative	Rare multiform PVC	Son of case 4 patient

BB = beta-blocker; CCB = calcium-channel blocker; CM = cardiomyopathy; F = female; JT = junctional tachycardia; M = male; PVC = premature ventricular contraction; VAD = ventricular assist device; VF = ventricular fibrillation; VT = ventricular tachycardia.

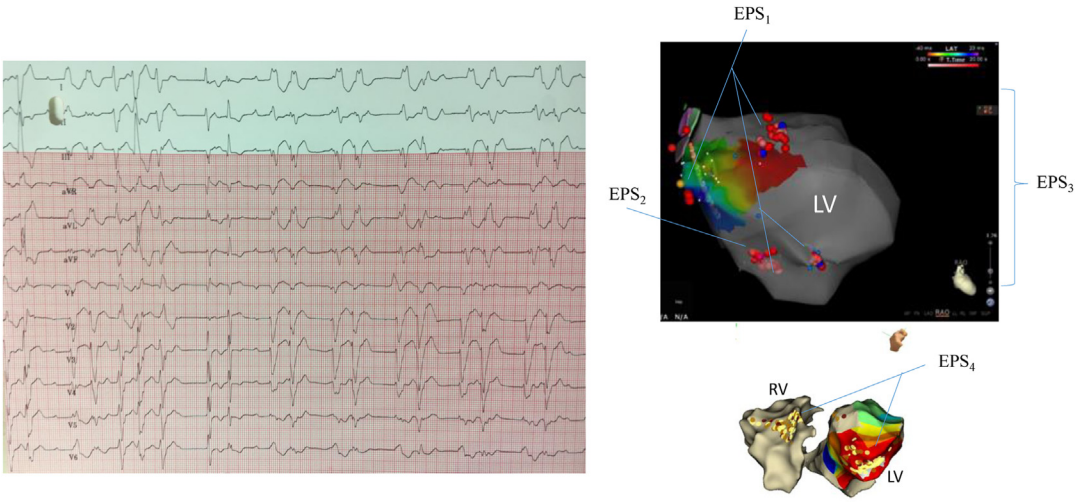

Figure 1 Case 1. Left panel: Premature ventricular contractions and nonsustained polymorphic ventricular tachycardia. Right upper panel: Composite figure for electrophysiology studies (EPS) ($EPS_{1–3}$; see text for each targeted site). Right lower panel: EPS_4: failed ablation sites. LV = left ventricle; RV = right ventricle.

sites) were targeted (Figure 1, right upper panel; a composite figure for $EPS_{1–3}$).

In EPS_2, a left posteromedial fascicular PVC was ablated. In EPS_3 we performed extensive HPS ablation until achieving a complete atrioventricular (AV) block with an RB escape rhythm. A biventricular implantable cardioverter-defibrillator was implanted. Six hours later, slow nonsustained VT (100 beats/min) reappeared.

In EPS_4 (Figure 1, right lower panel), multiple ablations at the right ventricle (RV) moderator band and the LV posteromedial papillary muscle all failed. Amiodarone was started and his VT subsided. He continued to have bigeminal PVCs and developed sustained ventricular fibrillation (VF) refractory to implantable cardioverter-defibrillator shocks and finally converted by an external defibrillation. He required biventricular assist devices. Three days later he developed drug-refractory sustained VF. He was placed on transplant list but died of ventricular assist device malfunction.

The genetic testing showed a pathogenic variant of the *SCN5A* gene (p.Arg814Trp) in exon 16. This was a de novo mutation, as targeted testing for the family was negative and there was no family history of heart disease or arrhythmias.

Case 2

A 15-year-old patient complained of palpitations and exertional shortness of breath. The ECGs showed polymorphic PVCs with relatively narrow QRS and later found relatively wide QRS PVCs (Figure 2, upper panel). Holter monitoring showed a ventricular ectopy burden of 67.3% with nonsustained polymorphic VT (longest 599 beats, fastest 176 beats/min), compatible with the diagnosis of MEPPC. A stress test showed the ventricular ectopy was suppressed at peak exercise. Echocardiogram showed mildly enlarged LV with mildly decreased LV EF (53%). Metoprolol did not improve her ventricular ectopy burden. Ivabradine 7.5 mg twice daily (BID) also failed. Flecainide 100 mg BID alone eliminated almost all her ventricular ectopy. In the follow-up, her cardiac function was normalized.

Genetic testing showed a variant in the *SCN5A* gene (p.Arg222Gln).

Case 3

The patient in case 3 is the brother of the patient in case 2. He was detected from family screening. His ECG and Holter both showed frequent multifocal ventricular ectopy (23.4%) (Figure 2, middle panel) in couplets, triples, and nonsustained VT, consistent with MEPPC. Metoprolol had no effect, but flecainide dramatically decreased the ventricular ectopy burden to 0.01%.

He and his mother both have the same *SCN5A* gene as his sister (case 2). The mother had palpitations but has not been seen by a cardiologist. Other family members were healthy and without arrhythmia issues. Their gene testing was not done.

Case 4

A 15-year-old female patient with type 3 polyglandular autoimmune syndrome came to the emergency room with incessant wide QRS VT and ventriculoatrial dissociation (VT_1). Cardiac magnetic resonance imaging revealed a reduced function (LV EF 32%) without evidence of myocarditis or scar. She had 7 ablations spanning over 3 years (Figure 3).

In $EPS_{1–3}$ both the RV and LV voltage maps appeared normal. VT_1 was ablated at the RV midseptal site and at the anterior RV septum 2 cm under the pulmonary valve with pre-QRS fascicular signals (Figure 3, left upper panel). In EPS_4, VT_2 was ablated at the left anterior fascicle (Figure 3, right upper panel). In EPS_5, VT_3 was ablated at the left bundle, and she developed complete heart block

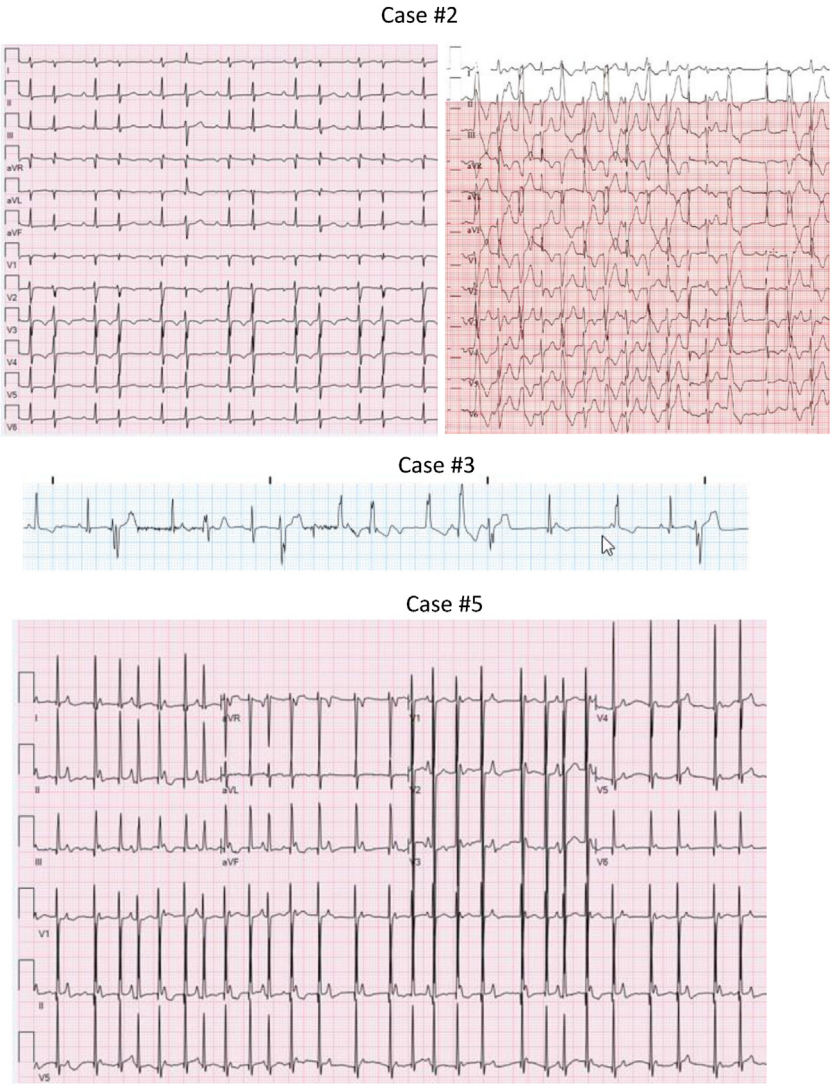

Figure 2 Upper panel (case 2): Electrocardiogram shows relatively narrow QRS (upper left panel) and relatively wide QRS (upper right panel) polymorphic premature ventricular contractions. Middle panel (case 3): Holter showed polymorphic ventricular ectopies and nonsustained ventricular tachycardia. Lower panel (case #5): Accelerated junctional rhythm with slightly varied QRS morphology and sinus morphology P wave with some sinus capture beats, vs sinus with frequent premature junctional contractions.

with junctional escape. A biventricular pacemaker was implanted. In EPS_6, VT_4 was eliminated at the proximal anteroseptal RV outflow tract. Cardiac biopsy at this site showed focal endocardial fibrosis without inflammation. This biopsy caused complete RBBB.

In EPS_7, ablation-induced AV nodal block, long HV interval with various HV conduction patterns, and intermittent HB tachycardia (VT_5) were noted (Figure 3, left lower panel). Isoproterenol induced an incessant HB tachycardia with 2:1 HV block (Supplemental Figure 1, upper panel). Mapping at the high septal LV outflow tract induced transient HV block and resulted in an HB tachycardia without associated A or V (Supplemental Figure 1, lower panel). Ablation at the subaortic aspect of the HB terminated VT_5. To eliminate all the HPS, additional ablation was performed at the right side at the HB site and the earliest ventricular depolarization at the septum (Figure 3, right lower panel). There was no more VT in 5 years of follow-up. Her ventricular function recovered completely.

There was no family history of cardiac arrhythmias or heart disease. She and her son (in case 5 below) both have negative genetic testing (comprehensive channelopathy and cardiomyopathy panel of 157 genes; Invitae, San Francisco, CA).

Case 5

The patient in case 5 is the son of the patient in case 4. He had prenatal diagnosis of double-inlet left ventricle with D-malposed great arteries and fetal arrhythmias. At birth, his ECG (before surgery) showed accelerated junctional rhythm with slightly varied QRS morphology and sinus morphology P wave with some sinus capture beats, vs sinus with frequent premature junctional contractions. There was no evidence of dual antegrade responses via fast and slow AV nodal

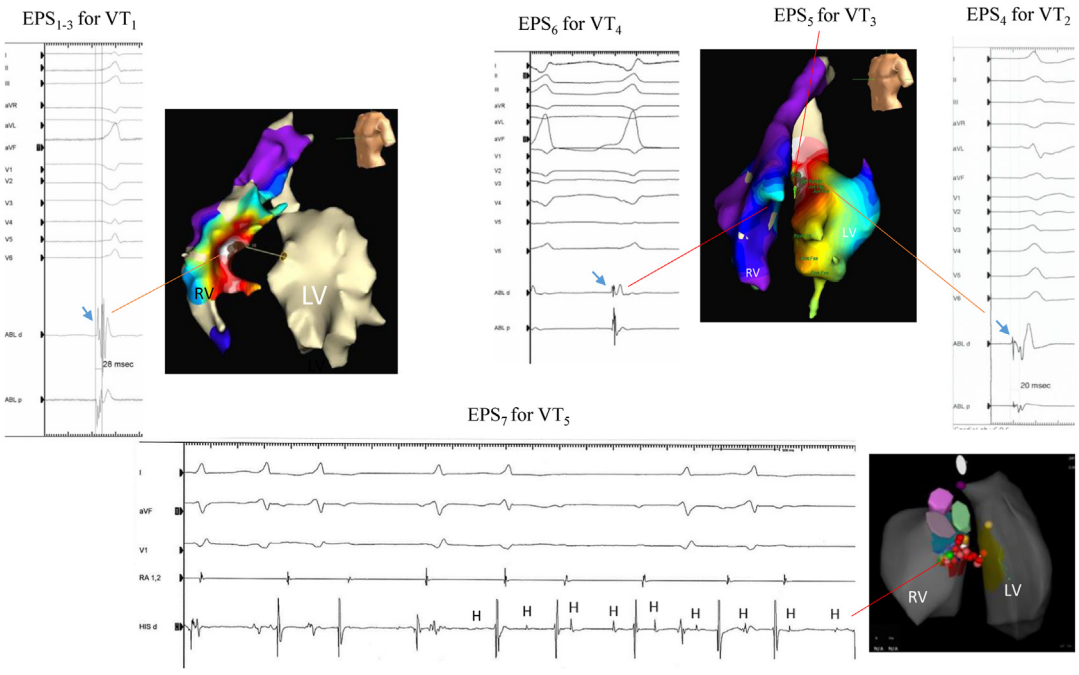

Figure 3 Case 4 electrophysiology studies (EPS) with ventricular tachycardia (VT) ablation sites. Left upper panel: $EPS_{1–3}$: VT_1 ablation sites. Right upper panel: $EPS_{4–6}$ for $VT_{2–4}$ ablation (details in text). Arrows indicate Purkinje spikes. Left lower panel: EPS_7 with His bundle tachycardia, complete atrioventricular block, and varied HV conduction. H = HB recordings). Right lower panel: VT_5 ablation sites. LV = left ventricle; RV = right ventricle.

pathways on numerous in-hospital telemetry monitors while he was admitted. Therefore, it was unlikely this could be sinus rhythm with dual antegrade responses via fast and slow AV nodal pathways (Figure 2, lower panel: MEPPC-like arrhythmia). Together with his mother's history (in case 4 above), he is also diagnosed with MEPPC. The tachycardia was not responsive to sotalol. However, ivabradine 0.1 mg/kg/dose BID completely suppressed his ectopy. He underwent a Norwood procedure at 1 month of age. Holter monitoring at 20 months of age showed rare isolated narrow QRS ectopy (burden 0.12%).

Discussion

The cardiac Purkinje system is known to cause ventricular ectopy, VT, and VF.[2] Laurent and colleagues[1] reported an autosomal dominant form of cardiac arrhythmia with multifocal ectopic premature Purkinje-related complexes (hence named MEPPC syndrome). MEPPC is characterized by frequent polymorphic PVCs of short coupling interval, sharp initial QRS deflection, relatively narrow QRS duration (Purkinje system hyperexcitability), and a family history and is associated with dilated cardiomyopathy.[2,4,5] Mutations in *SCN5A* genes were shown to be associated with MEPPC.[2] However, presence of an *SCN5A* variant is not required for the diagnosis.

We report 5 pediatric MEPPC cases in 3 families. In the 2 catheter ablation cases, the EPS mapping and ablation sites proved their multifocal HPS involvement. In 3 medically treated patients, their ECG/Holter patterns were compatible with MEPPC. The association of *SCN5A* gene in our cases 1–3 also contributes to the diagnosis. In case 4 extensive EPS proved the HPS origin of all the VTs. In case 5 the ECG/Holter features were suggestive of MEPPC, and the patient is related to the patient in case 4 (they are mother and son). Thus, even though they both had negative genetic testing, they are included in this case series, as some of the gene variants associated with MEPPC may still be elusive.

SCN5A gene encodes the main pore-forming sodium channel isoform α subunit Nav1.5, which mediates rapid Na^+ upstroke and causes fast depolarization and initiates action potential, resulting in rapid impulse propagation.[4] In the past 2 decades many MEPPC-causative *SCN5A* variants have been discovered.[1,5–8] The gain of function by p.Arg222Gln (R222Q) in our cases 2 and 3 and p.Arg814Trp (R814W) in our case 1 both increase the Na^+ entry through the α pore, causing early afterdepolarization of the HPS, resulting in its hyperexcitability.[1,9,10]

In the literature, quinidine, hydroquinidine, amiodarone, flecainide, or combination therapy all have been reported as treating MEPPC with success.[1,5–7,11–14] Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker, which acts by inhibiting the I_f channel, thereby reducing the heart rate.[15] We found that this relatively new drug can be useful in some of the MEPPC patients.

Leventopoulos and colleagues[12] reported 1 adult case of MEPPC treated medically with flecainide and stated that this syndrome is like a contemporary Lernaean Hydra in electrophysiology and ablation is likely ineffective, as there were multiple foci. In our case 4 we achieved a VT-free state after tenacious ablation efforts and the patient's cardiac function returned to normal. Thus, even a Lernaean Hydra of electrophysiology can potentially be cured.[11] However, in both of

our ablation cases the affected sites involved proximal HPS (HB, left bundle, and right bundle); thus we could not avoid ablation-induced heart block.

In our case 4, 1 of the multifocal tachycardias was from the HB, and this HB tachycardia persisted with both AH and HV block (HB tachycardia without associated A or V, ie, HB parasystole). Therefore, we suggest changing the name of this syndrome to multifocal ectopic premature "HPS-related" instead of "Purkinje-related" for this syndrome (MEPHPC, instead of MEPPC).

Conclusion

MEPPC should be considered in young patients with frequent multifocal PVCs with relatively narrow QRS. It may require extensive catheter ablations to achieve freedom from arrhythmias in severe cases, and ablation-induced heart block may be inevitable. Therefore, medications should first be tried, which may result in normalization of the LV function in at least some patients.

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Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2023.05.009.

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