

Infant Ventricular Fibrillation After ST-Segment Changes and QRS Widening A New Cause of Sudden Infant Death?

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Background—Ventricular arrhythmia–related sudden cardiac arrest in infants with structurally normal hearts is rare. There have been no previously published reports of infants <3 months of age with ventricular fibrillation in which a primary diagnosis could not be defined.

Methods and Results—Retrospective chart review of 3 unrelated infants <2 months of age from 3 different tertiary care centers within the United States and Australia was conducted. All 3 infants survived sudden cardiac arrest secondary to multiple episodes of polymorphic ventricular tachycardia and ventricular fibrillation. Each infant demonstrated unique and transient ECG findings consisting of ST changes and QRS widening before arrhythmia onset, which have not been previously reported. Amiodarone, sedation, sodium channel–blocking agents, and ventricular pacing were effective in suppressing acute events. Despite thorough investigation, including genetic testing, the cause of ventricular arrhythmias in each of these infants remains unclear.

Conclusions—This is the first report of idiopathic ventricular fibrillation in young infants preceded by stereotypical transient ECG changes. These findings may represent a new, potentially treatable cause of sudden infant death. Recognition of these prodromal changes may be important in future management and survival of these infants. (*Circ Arrhythm Electrophysiol.* 2013;6:712-718.)

Key Words: electrocardiography ■ heart arrest ■ pediatric ■ tachycardia, ventricular ■ ventricular fibrillation

Cardiac arrest secondary to ventricular arrhythmias is rare in infants with structurally normal hearts.¹ Infants with this dramatic presentation are often diagnosed with a cardiac tumor, metabolic disorder, or primary electric disease.²⁻⁹ There have been no previous reports of young infants with ventricular fibrillation (VF) in which a primary diagnosis could not be determined. We present 3 unrelated infants <2 months of age who survived VF arrests. In each infant, VF was preceded by unique ECG changes that have not been previously described. We have been unable to confirm a diagnosis in any of the infants. The purpose of this report is to describe a new potential cause of sudden infant death.

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Case 1

A 5-week-old term Southeast Asian female infant presented with episodes of unresponsiveness and cyanosis after a feed at home. In the emergency room, she was found unresponsive and in polymorphic ventricular tachycardia (PMVT). Intravenous

lidocaine and magnesium were ineffective. Direct current countershock was transiently effective, but recurrent PMVT and VF required a total of 6 shocks and loading of amiodarone (5 mg/kg) before maintenance of sinus rhythm. The evaluation, including history, physical examination, metabolic screen, ECG (Figure 1), echocardiogram, cardiac MRI, and coronary angiography, was normal. There was no history of intercurrent illness or evidence of an infectious process. An electrophysiology study demonstrated no inducible arrhythmias at baseline or on isoproterenol. The family history was unremarkable.

She continued to have recurrent PMVT/VF episodes, some but not all associated with adrenergic stimulation. She, therefore, underwent left cardiac sympathetic denervation and placement of an epicardial implantable cardioverter defibrillator. Three weeks after the initial VF event, she was discharged home on propranolol (4 mg/kg per day), but was readmitted 1 week later with recurrence of VF. During the ensuing 3 weeks, she had >30 VF episodes. At least 2 minutes before each VF episode, preceding ECG changes were noted beginning with

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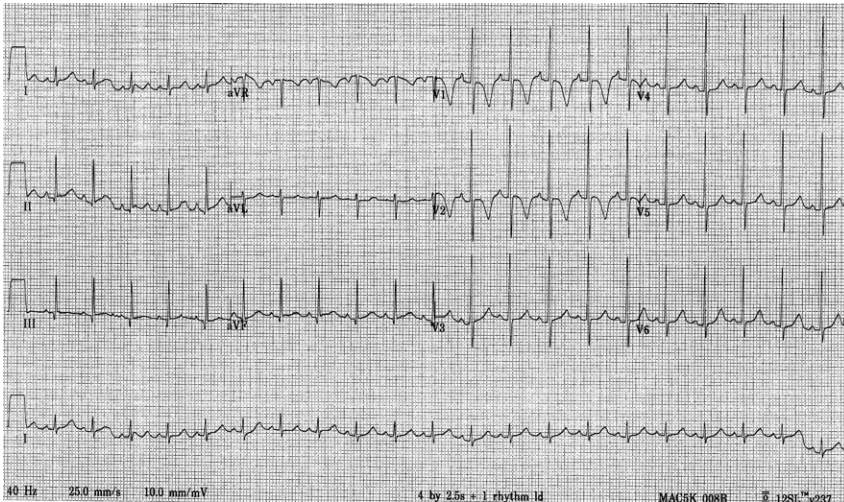


Figure 1. Baseline ECG, case 1.

diffuse ST depression. ST depression was followed by QRS widening (1.5 minutes before VF) and either premature ventricular contractions (PVCs) or salvos of PMVT (30 seconds before VF; Figure 2). These ECG changes resolved within several minutes of VF termination, which always required direct current cardioversion. Different antiarrhythmic combinations were attempted, including amiodarone, lidocaine, mexiletine, esmolol, flecainide, verapamil, and propranolol. As a result of potential coronary vasospasm, intravenous nitroglycerin and

verapamil were administered, but did not affect ST segments nor prevent progression to VF. A trial of ventricular pacing at 140 beats per minute was performed during prodromal ST changes and aborted the progression to VF arrest. Genetic testing for long-QT syndrome, catecholaminergic PMVT, and Brugada syndrome was negative (Table).

She was discharged home on amiodarone 16 mg/kg per day, propranolol 5 mg/kg per day, verapamil 2.7 mg/kg per day (because of potential coronary vasospasm), and VVI pacing at

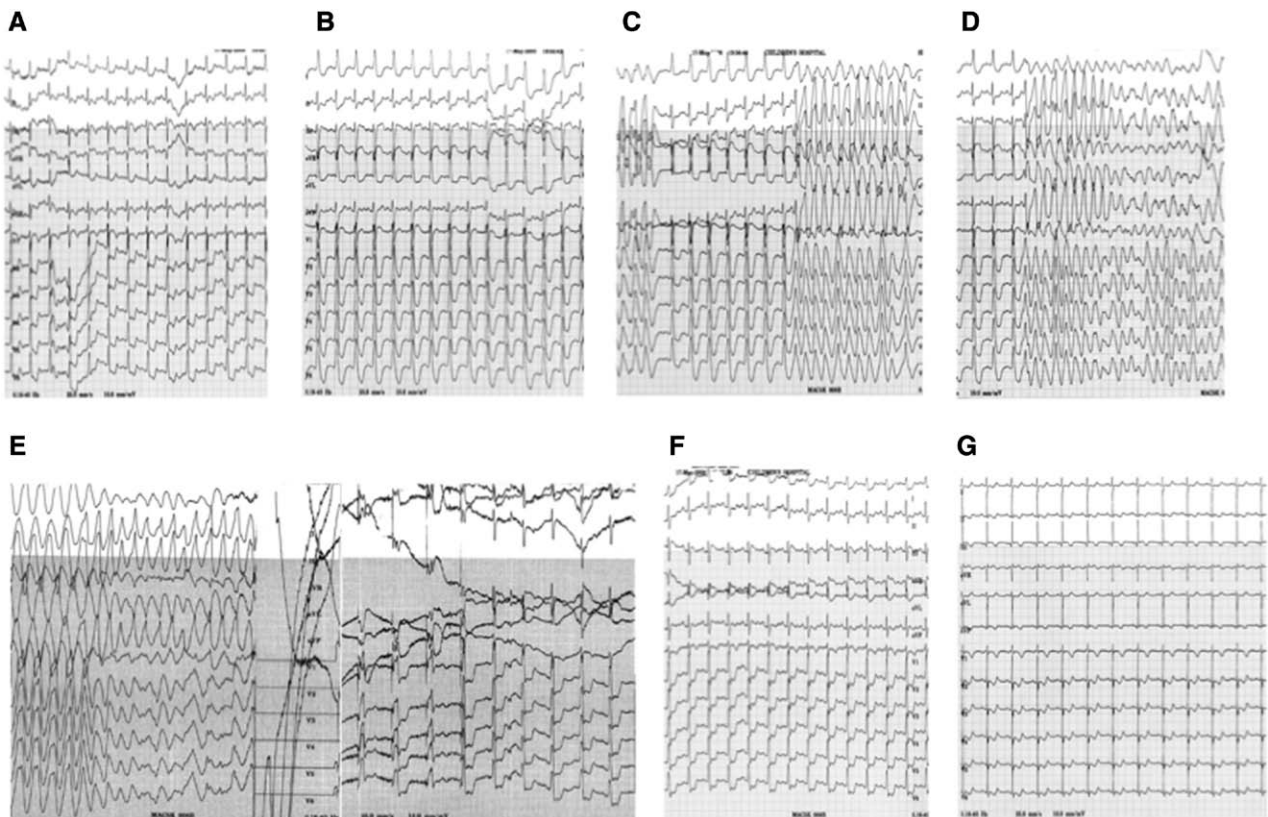


Figure 2. ECG tracings, case 1. **A**, 1.5 minutes before ventricular fibrillation (VF)—sinus rhythm with narrow QRS and ST depression. **B**, 1 minute before VF—the QRS is widening and ST depression is increasing. **C**, 30 seconds before VF—salvos of polymorphic ventricular tachycardia (VT). **D**, Sustained polymorphic VT. **E**, Direct current cardioversion successfully terminates VF. Sinus rhythm returns with persistent widening of QRS and ST depression. **F**, 30 seconds after defibrillation—the QRS is narrowing but ST depression persists. **G**, 2 minutes after defibrillation—the QRS is narrow and the ST depression is resolving.

Table. Summary of Genetic and Metabolic Testing

	Case 1	Case 2	Case 3
Genetic testing	<ol style="list-style-type: none"> 1. KCNE1 2. KCNE2 3. KCNH2 4. KCNQ1 5. RYR2 6. SCN5A 	<ol style="list-style-type: none"> 1. AKAP9 2. ANK2 3. CACNA1C 4. CACNB2 5. CASQ2 6. CAV3 7. GPD1L 8. KCNE1/KCNE2 9. KCNH2 10. KCNJ2 11. KCNQ1 12. RYR2 13. SCN1B/SCN4B 14. SCN5A 15. SNTA1 16. LQT Exon Array 	<ol style="list-style-type: none"> 1. ACTN3 2. AKAP9 3. ANK2 4. CACNA1C/CACNA1B 5. CACNB2 6. CASQ2 7. CAV3 8. GPD1L 9. KCNE1/KCNE2/KCNE3 10. KCNH2 11. KCNJ2 12. KCNQ1 13. MYLK3 14. RYR2 15. SCN1B/SCN3B/SCN4B 16. SCN5A 17. SLC25A3 18. SNTA1
Metabolic testing	<ol style="list-style-type: none"> 1. Urine amino acids 2. Ammonia level Newborn screening: <ol style="list-style-type: none"> 1. Amino acid disorders 2. Organic acid disorders 3. FAO disorders: <ol style="list-style-type: none"> CUD CPT-1 deficiency CPT-2 deficiency CACT LCHAD deficiency MCAD deficiency M/SCHAD deficiency MCKAT SCAD deficiency TFP deficiency VLCAD deficiency DE-RED GA-II GALE GALK 	<ol style="list-style-type: none"> 1. Plasma amino acids 2. Plasma carnitine levels 3. Acylcarnitine profile 4. Urine amino acids 5. Urine carnitine Newborn screening: <ol style="list-style-type: none"> 1. Amino acid disorders 2. Organic acid disorders 3. FAO disorders: <ol style="list-style-type: none"> CUD CPT-1 deficiency CPT-2 deficiency LCHAD deficiency MCAD deficiency M/SCHAD deficiency MAD deficiency SCAD deficiency TFP deficiency VLCAD deficiency FIGLU disorder 	<ol style="list-style-type: none"> 1. Urine amino acids Newborn screening: <ol style="list-style-type: none"> 1. Amino acid disorders 2. Organic acid disorders 3. FAO disorders: <ol style="list-style-type: none"> CUD CPT-1 deficiency CPT-2 deficiency CACT LCHAD deficiency MCAD deficiency M/SCHAD deficiency MAD deficiency VLCAD deficiency

CACT indicates carnitine acylcarnitine translocase; CPT-1, carnitine palmitoyl transferase deficiency type 1; CPT-2, carnitine palmitoyl transferase deficiency type 2; CUD, carnitine uptake defect/carnitine transporter defect; DE-RED, dienoxy-coenzyme A reductase; FAO, fatty acid oxidation; FIGLU, formiminoglutamic acid disorder; GA-II, glutaric acidemia type 2; GALE, galactose epimerase; GALK, galactokinase; LCHAD, long-chain hydroxyacyl coenzyme A dehydrogenase deficiency; LQT, long QT; MAD, multiple acyl-coenzyme A dehydrogenase deficiency; MCAD, medium-chain acyl-coenzyme A dehydrogenase deficiency; M/SCHAD, medium/short-chain L-3-hydroxy acyl-coenzyme A dehydrogenase deficiency; MCKAT, medium-chain ketoacyl-coenzyme A thiolase; RYR2, ryanodine receptor; SCAD, short-chain acyl-coenzyme A dehydrogenase deficiency; TFP, trifunctional protein deficiency; and VLCAD, very long-chain acyl-coenzyme A dehydrogenase deficiency.

a rate of 130 beats per minute. Ventricular pacing was weaned slowly over time. The patient is now 5 years old and remains on atenolol (0.2 mg/kg per day) only, without any further episodes of ventricular arrhythmia.

Case 2

A 2-week-old term Hispanic female was found shortly after a feed to be unresponsive and cyanotic. She was taken to a fire station where emergency medical services found her in VF. Defibrillation was transiently successful with eventual return of sinus rhythm after the sixth shock. During the course of 2 hours in the emergency room, she had 3 separate VF episodes, each preceded by stimulation (laboratory draw, ECG lead placement, and bed transfer). Intravenous magnesium was ineffective. After

the third VF episode, 2.5 mg/kg of amiodarone was given without further recurrence. She was administered another 2.5 mg/kg bolus, started on an amiodarone drip, and remained in sinus rhythm for 20 hours, after which the amiodarone was discontinued. One hour later, during endotracheal tube suctioning, she had another VF episode. Single-lead telemetry of this episode (Figure 3A–3F) demonstrated ST elevation (although all other episodes demonstrated ST depression, see Figure 3G), QRS widening, and salvos of PMVT minutes before VF with return to a normal ECG within several minutes after VF termination. She was cardioverted with direct current, restarted on amiodarone, and transferred to a tertiary care center. After arrival (15 hours after her last VF episode), a nasal swab procedure resulted in recurrent VF, requiring extracorporeal membrane oxygenator



Figure 3. Telemetry tracings, case 2. **Top** and **bottom** panels are a continuation of rhythm over time. **A**, 3 minutes before ventricular fibrillation (VF)—ST changes are noted. **B**, 2 minutes before VF—progressive ST changes. **C**, 1.5 minutes before VF—QRS begins to widen progressively. **D**, 1 minute before VF—QRS remains wide. There are short salvos of ventricular tachycardia (VT) between sinus rhythm. **E**, Initiation of sustained polymorphic VT. **F**, Successful defibrillation of VF. **G**, A separate episode demonstrating ST depression before onset of VT/VF.

support because of pulseless electric activity after consecutive shocks. She subsequently underwent left cardiac sympathetic denervation and placement of an epicardial implantable cardioverter defibrillator. Transient harlequin flushing was noted after left cardiac sympathetic denervation. Her evaluation, including ECG (Figure 4), echocardiogram, coronary angiography, infectious workup, and metabolic testing, was normal. The family history was unremarkable. Commercial genetic testing (Table) for long-QT syndrome, catecholaminergic PMVT, and Brugada syndrome demonstrated no definitive pathogenic mutation. She was discharged home on amiodarone (3 mg/kg per day) and propranolol (5 mg/kg per day). Steady rate ventricular pacing could

not be performed as a result of lack of ventriculo-atrial conduction and relatively elevated heart rates (140 beats per minute).

Three days after discharge, she was readmitted because of maternal concerns. No VF events were recorded on her implantable cardioverter defibrillator. Per parental request, she received routine immunizations. Six hours after immunizations and during the subsequent 24 hours, she had 13 episodes of VF. One episode was related to a diaper change, but the remaining were not associated with stimulation. Esmolol boluses and infusion (300 µg/kg per minute) were not effective in preventing VF. The arrhythmia was acutely controlled with sedation (midazolam and propofol). She was discharged home

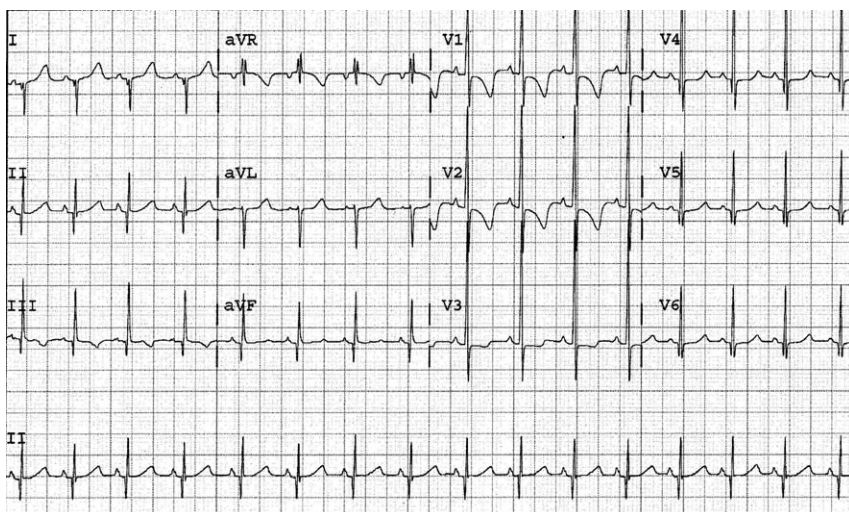


Figure 4. Baseline ECG, case 2.

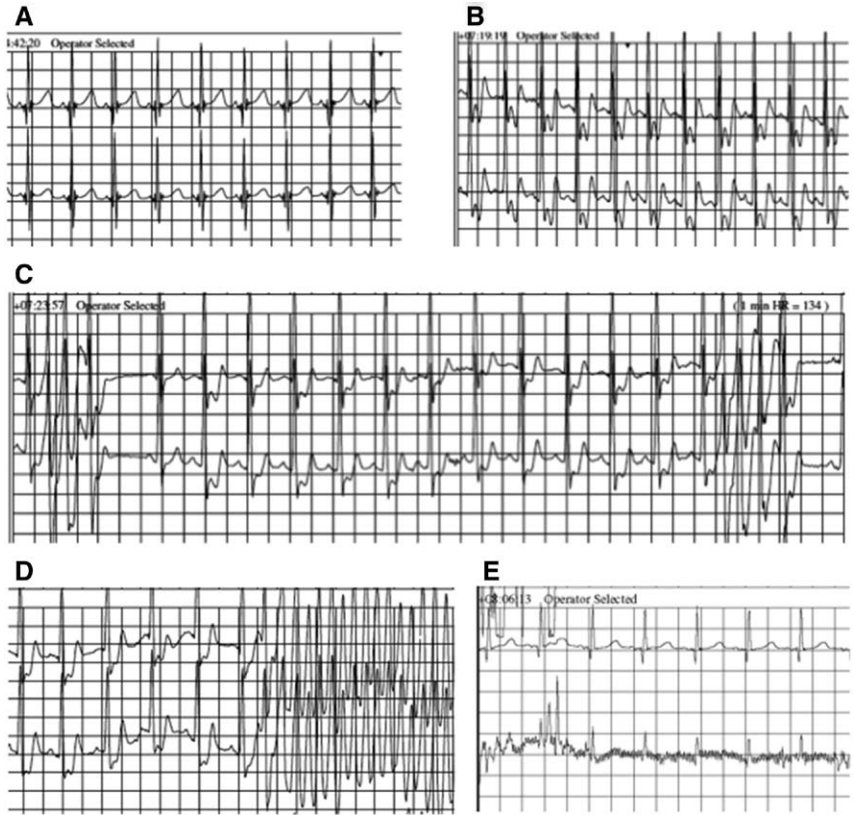


Figure 5. Event monitor tracings, case 3. **A**, 37 minutes before ventricular fibrillation (VF)—baseline sinus rhythm with narrow QRS and normal ST segments. **B**, 4 minutes before VF—QRS widening and ST depression. **C**, 37 seconds before VF—nonsustained polymorphic ventricular tachycardia (VT). **D**, Sustained polymorphic VT. **E**, 25 minutes after defibrillation—normal sinus rhythm with return of narrow QRS and ST segments.

on amiodarone (4 mg/kg per day) and propranolol (7 mg/kg per day), with no recurrences in 17 months of follow-up.

Case 3

A 5-week old term white male with a history of intrauterine growth retardation (birth weight 2.5 kg) and feeding difficulties was admitted after a feed-related episode of pallor, cyanosis, and decreased tone. In the hospital, he had 2 similar episodes not associated with feeds. The following day, cardiac monitoring demonstrated VF, which was terminated by a single direct current countershock. The infant was placed on dobutamine and lidocaine and transferred to a tertiary care

center. The infant remained stable for 48 hours, and the dobutamine and lidocaine were discontinued. During the ensuing 3 days, he had 3 more episodes of VF (separated by 24 and 8 hours) requiring defibrillation, each preceded by similar transient ST depression, QRS widening, short-coupled PVCs, and salvos of PMVT before degeneration into VF (Figure 5). The infant was treated with esmolol and atenolol. Evaluation, including ECG (Figure 6), echocardiogram, coronary angiography, infectious workup, and metabolic workup, was normal (Table). There was no family history of arrhythmias or sudden death. Eleven days later, the infant had a recurrence of VF. The esmolol was discontinued. As a result of short coupling

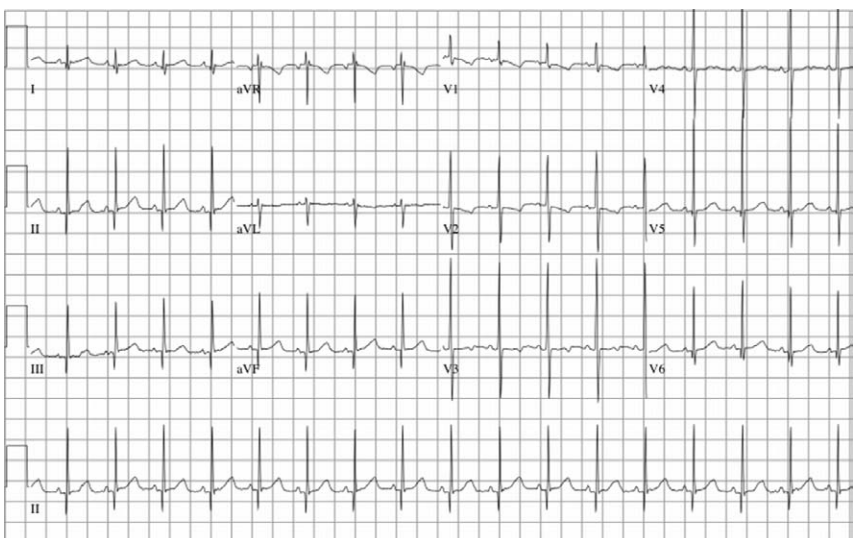


Figure 6. Baseline ECG, case 3.

of PVCs, quinidine (hydroquinidine 6 mg/kg per dose q8) was added in addition to atenolol, and an epicardial implantable cardioverter defibrillator was placed. Genetic testing was performed on 69 genes in a cardiac panel and included 23 arrhythmia genes with no definitive causative mutation found. He is currently alive and well on atenolol and quinidine, with no further VF episodes in 18 months of follow-up.

Discussion

We describe 3 young infants (<6 weeks of age) with recurrent VF, each preceded by unique and transient ECG changes. ST changes and QRS widening 2 to 5 minutes before VF are followed by PVCs or PMVT 30 seconds to 1 minute before VF. There is complete resolution of ST segments and QRS widening within minutes after successful defibrillation, with recurrence of ST and QRS changes before each VF episode. These prodromal ECG changes have not been previously described. We think that clinical recognition of this new syndrome with newly described, stereotypical ECG changes preceding ventricular arrhythmia may define a new cause of sudden infant death that has not been previously known.

Previous literature of infants with structurally normal hearts surviving VF is sparse. The most common cause is long-QT syndrome, with most of these infants having significant QT prolongation.⁶⁻⁸ Among infants with normal resting ECGs, Brugada or Brugada-like syndrome seems to be the most common cause,²⁻⁴ although some of these infants may demonstrate intermittent ST changes or intraventricular conduction delay. Kanter et al² found disease-causing mutations in SCN5A or CaCNB2b channels in 5 infants with ventricular tachycardia or VF, in whom a diagnosis could not be initially determined. The only reported case of an infant with VF and ECG changes had ST depressions and atrioventricular block before VF. This 3-month-old infant was diagnosed with suspected coronary ischemia and treated for a possible fatty acid oxidation disorder, but ultimately a diagnosis was never confirmed.⁵ Although none of the infants in our report had atrioventricular block, the ST changes and lack of diagnosis may suggest a similar disease process.

Despite thorough evaluation, we have been unable to determine a diagnosis in any of the 3 infants. All had structurally normal hearts with normal myocardial function. Metabolic workup was negative. Family history was benign in all 3 infants, suggesting possible *de novo* genetic mutations. Genetic testing has not been revealing. Resting ECGs were normal, with no evidence of long- or short-QT syndrome, Brugada syndrome, early repolarization, or J-wave syndromes. None of the infants was febrile or ill, and infectious workup was negative. None of the infants underwent provocative procainamide or ajmaline testing for Brugada syndrome; in 2 of the infants, clinical status was deemed too tenuous for testing, and in the third infant flecainide did not result in ECG changes consistent with the disease. Furthermore, amiodarone, which can potentiate arrhythmias in Brugada syndrome, seemed to help terminate acute VF events in cases 1 and 2. Our interim diagnosis, therefore, is idiopathic VF, an entity that has been described in adults but not in infants. The mode of onset of VF seen in each of these infants has never been described in the adult.¹⁰

The reason for ECG changes before VF is not clear. In each case, coronary ischemia was suspected; however, coronary angiography was normal in all 3 infants. Transmural or subendocardial ischemia may cause ST-segment changes and QRS widening; however, ischemia-induced QRS widening is secondary to marked prolongation of the R wave which leads to a tombstone configuration, not seen in the 12-lead ECG obtained for case 1.^{11,12} Furthermore, such marked ECG changes are not typical of transient coronary vasospasm. Although none of the infants underwent provocative testing for coronary spasm and, therefore, transient ischemia cannot be ruled out, coronary vasodilators did not resolve ST changes or prevent VF in case 1.

Based on the ST changes and QRS widening, as well as response to sodium channel blockade, we hypothesize involvement of the sodium ion channel and suggest that additional ions or ion channels may be involved. Inhibition of the Na+K+ATPase pump has been shown to result in accumulation of both intracellular sodium and calcium (via activation of the Na+Ca+ exchanger).¹³ Dysregulation of the Na+K+ATPase or Na+Ca+ exchanger may thus result in both Na and Ca imbalances, leading to transient QRS widening and ST changes that would not have been identified by genetic testing performed. The intermittent arrhythmia onset, sometimes related to feeds or stimulation and reduced by sedation, may also suggest some influence by the autonomic nervous system or alternatively an energy-dependent substrate, such as ATP. The absence of arrhythmia recurrence after 3 months of age may represent a developmental or maturational process resulting in functional recovery over time.

With regard to treatment, VF events seemed to be best suppressed acutely with amiodarone infusion, sodium channel-blocking agents, sedation, and steady rate ventricular pacing. β -1 blockade alone and left cardiac sympathetic denervation did not prevent VF episodes. Although follow-up is relatively short in 2 of the infants, all 3 are alive without further arrhythmias. Genetic analysis was limited to known arrhythmia-causing mutations. In the future, more exhaustive testing, such as whole-genome sequencing, is needed and may uncover the genetic basis for this potentially new infant arrhythmic sudden death syndrome. Recognition of these characteristic prodromal ECG changes before VF may be important in the management and survival of these young infants.

Limitation

This is a retrospective review of young infants from different centers. A full 12-lead ECG immediately before VF was obtained in only 1 of the infants (case 1), and therefore, we cannot determine whether the ST changes for the other 2 infants were definitely ST elevation versus depression. Although none of the infants was suspected to have a metabolic disorder and newborn screening testing was relatively comprehensive in all, extensive metabolic testing was not performed. Genetic testing was limited and did not include whole-exome or whole-genome sequencing; therefore, we cannot definitively conclude whether these infants represent a new disease.

Disclosures

None.

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CLINICAL PERSPECTIVE

We report a potentially new arrhythmia syndrome in 3 unrelated infants manifest as polymorphic ventricular tachycardia and ventricular fibrillation, immediately preceded by transient ST changes and QRS widening. All infants have survived with therapy. This syndrome may represent a newly recognized, potentially treatable cause of sudden infant death. Recognition of the prodromal ECG changes by clinicians may be important in the future management and survival of these infants.