

Ventricular fibrillation due to a likely pathogenic *SOS1* variant: An unrecognized etiology of infantile sudden death?



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Introduction

We present the case of a female infant presenting after a ventricular fibrillation arrest found to have ectopic atrial tachycardia (EAT). Evaluation revealed a likely pathogenic variant in *SOS1* not previously reported in affected individuals. *SOS1* variants are associated with Noonan syndrome, which belongs to a family of related genetic syndromes affecting the RAS/MAPK signaling pathway. To date, this is the first case reported of a ventricular fibrillation arrest in a patient with a RASopathy-related variant prior to development of the typically associated structural cardiac phenotype and may represent a previously unrecognized etiology of sudden death during infancy.

Case report

An 8-week-old former 36-week female infant presented following a documented ventricular fibrillation arrest at home. The patient was at her baseline health the previous day; however, she did not rouse for her usual morning feed. She was found limp and pale with agonal breathing in her bassinet. Rescue breaths were initiated and on arrival Emergency Medical Services noted the patient to be pulseless. Cardiopulmonary resuscitation was initiated and an external defibrillator revealed coarse ventricular fibrillation (Figure 1a). Initial shock of 10 J was given with conversion to an atrial rhythm with aberrant ventricular conduction. The patient developed increasing frequency of ectopy (Figure 1b) before degenerating to ventricular fibrillation. A second shock with 20 J was unsuccessful. A third shock of 20 J successfully converted the rhythm to sinus with aberrant ventricular

KEY TEACHING POINTS

- RASopathies can present with an arrhythmia phenotype that precedes other typical structural cardiac findings of valvular disease or hypertrophic cardiomyopathy.
- Complex ventricular ectopy is a rare finding in RASopathies; however, it may result in unexpected sudden cardiac death.
- Genetic testing in infantile aborted sudden cardiac death is important, as arrhythmia phenotypes can present prior to typical syndrome findings.

conduction and atrial ectopy (Figure 1c) with return of spontaneous circulation. No epinephrine or amiodarone was given during the resuscitation. Review of the defibrillator tracings show 14 minutes from pad placement to ROSC and total arrest time was estimated at 20 minutes.

On arrival in the ICU the patient was found to have incessant, nonsustained EAT (Figure 2a) with ventricular rates up to 300 beats per minute in the setting of seizure activity. Intravenous lorazepam was given with cessation of seizure activity and amiodarone boluses were given (total 5 mg/kg), with transient establishment of sinus rhythm. The QTc was noted to be >500 ms (Figure 2b) and Brugada positioning of leads was unrevealing. Transthoracic echocardiogram demonstrated a structurally normal heart with normal valve morphology and a patent foramen ovale with left-to-right flow. The initial ejection fraction was 49% and there was no ventricular hypertrophy, dilation, or noncompaction noted (Figure 3). The patient was started on an esmolol infusion titrated to 225 mcg/kg/min with frequent, nonsustained breakthrough of EAT. Over the next 24 hours there was normalization of the QTc interval with normal T-wave morphology (Figure 2c). A procainamide challenge was performed and was negative. Cardiac magnetic resonance imaging showed normalization of ventricular function

KEYWORDS Ectopic atrial tachycardia; Noonan syndrome; Pediatric; RASopathy; *SOS1*; Ventricular fibrillation (Heart Rhythm Case Reports 2021;7:510–513)

Conflict of Interest: The authors have no conflicts of interest to disclose. **Funding:** The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. **Address reprint requests and correspondence:** Dr Christopher W. Follansbee, Ward Family Heart Center, Children's Mercy Hospital Kansas City, 2401 Gillham Rd, Kansas City, MO 64108. E-mail address: cwfollansbee@cmh.edu.

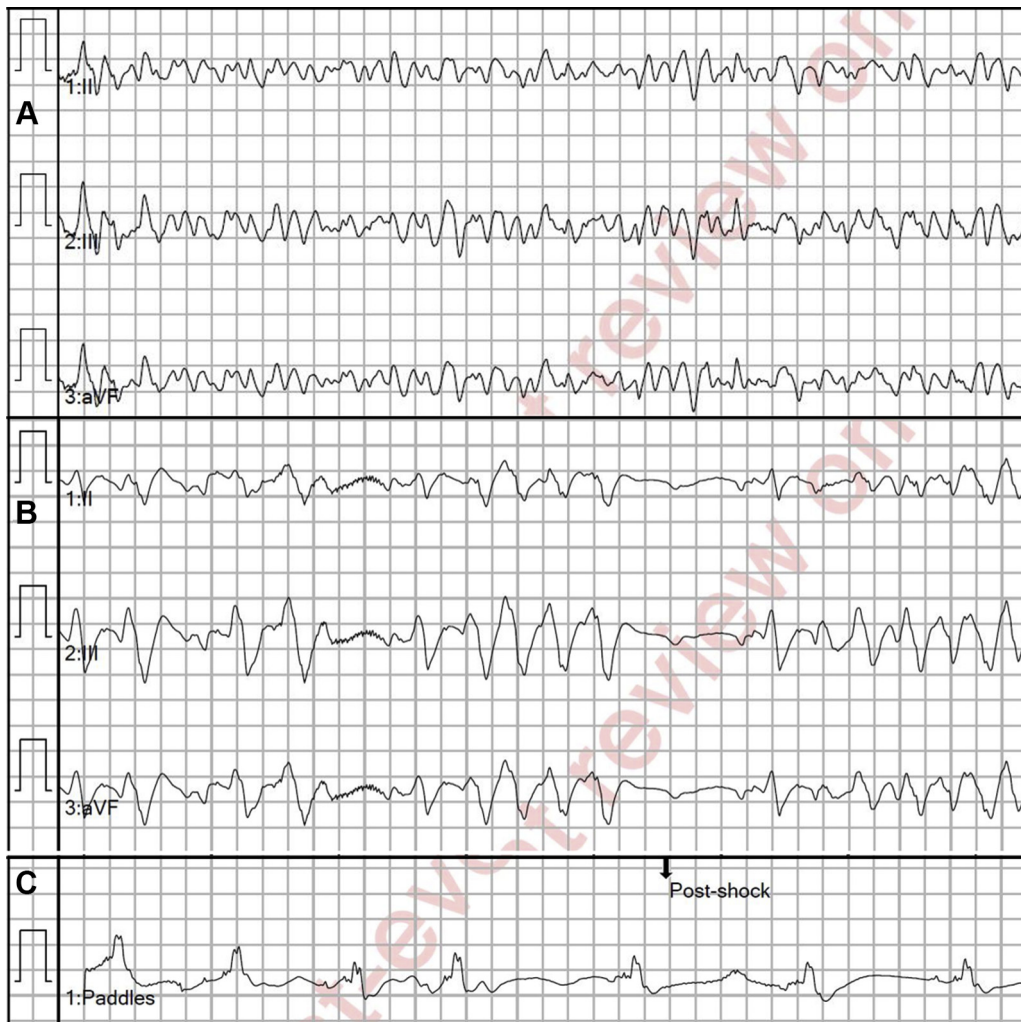


Figure 1 A: The initial rhythm recorded on external defibrillator demonstrating coarse ventricular fibrillation. B: After initial defibrillation, rhythm strip demonstrating increasing burden of ectopy preceding degeneration to ventricular fibrillation. C: Rhythm following third defibrillation demonstrating probable sinus rhythm with atrial ectopy and aberrant ventricular conduction.

without late gadolinium enhancement. Esmolol was titrated to 400 mcg/kg/min with continued occasional nonsustained breakthrough. The patient was transitioned to sotalol that was titrated to 6.8 mg/kg/day (132 mg/m²/day), with only rare nonsustained breakthrough achieved by day 5.

Laboratory evaluation included an initial capillary blood gas remarkable for acidosis with pH 7.21, pCO₂ 25 mm Hg, HCO₃ 22 mmol/L, and base excess -14 mmol/L. Lactate was 0.9 mmol/L with glucose 86 mg/dL. Normal results were found for complete blood count with differentiation, basic metabolic panel, liver function panel, thyroid function panel, cortisol level, erythrocyte sedimentation rate, and C-reactive protein. Severe acute respiratory syndrome coronavirus 2 screen was negative. Metabolic evaluation included an unremarkable urine organic acids and acylcarnitine profile.

The genetics team was consulted and a standard 3-generation family history was obtained with the proband the second biological child of the parents. The older sibling was 2 years old and without known medical conditions. The mother had history of pancreatic cancer status post resection

and chemotherapy. The paternal grandfather died of a presumed myocardial infarction in the fifth decade of life; however, no autopsy was performed. There was no family history of congenital heart disease, arrhythmia, sudden death, cardiomyopathy, recurrent syncope, congenital deafness, seizure, miscarriage, or developmental delay. Electrocardiograms were obtained on the parents and were normal. Genetic testing was performed using a comprehensive arrhythmia and cardiomyopathy NGS panel with maternal and paternal segregation studies. This revealed a *de novo* likely pathogenic (PS2, PM2, PM5, PP3) variant c.1649T>G (p.Leu550Arg) in *SOS1* (GRCh37/UCSC hg13: 2-39249920-A-C). Owing to the presentation of aborted sudden cardiac death, the patient underwent dual-chamber epicardial implantable cardioverter-defibrillator implantation prior to discharge.

Discussion

We present a case of aborted sudden cardiac death in a previously healthy infant found to have a likely pathogenic *SOS1*

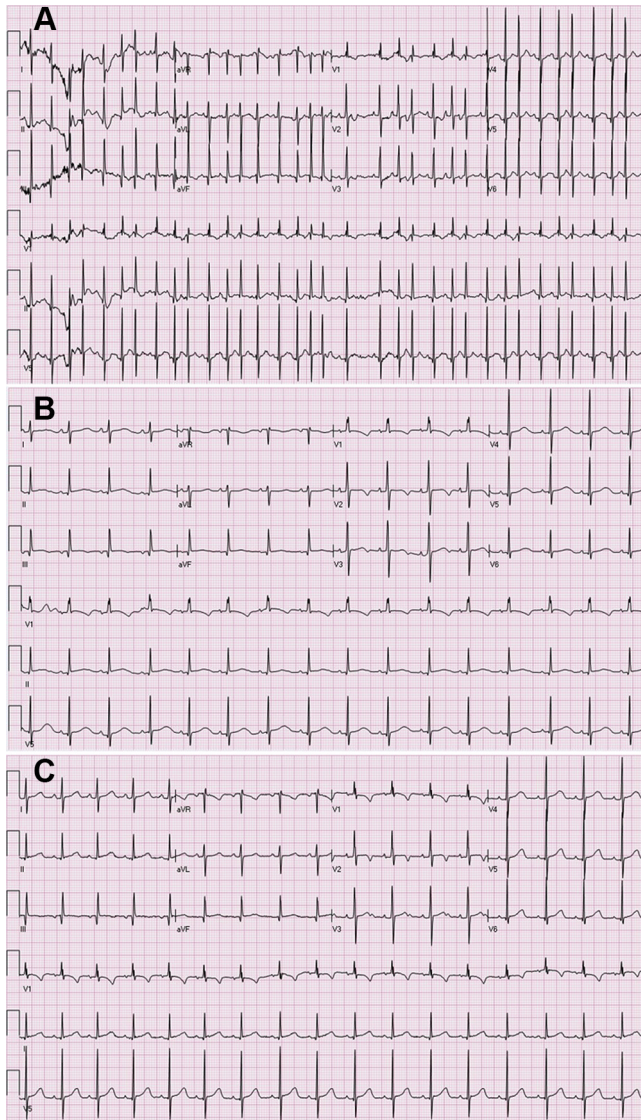


Figure 2 A: Initial 12-lead electrocardiogram (ECG) on arrival in the intensive care unit, demonstrating frequent nonsustained episodes of ectopic atrial tachycardia. B: A 12-lead ECG obtained following conversion to sinus rhythm with a 5 mg/kg amiodarone bolus showing a prolonged QTc. C: A 12-lead ECG obtained 24 hours after presentation showing normalization of the QTc and T-wave morphology.

variant, incessant EAT, without typical phenotypic findings of Noonan syndrome. This case reports novel findings of disease associated with this *SOS1* variant as well as a documented ventricular fibrillation arrest in a RASopathy prior to development of typical structural cardiac phenotypic findings.

The RASopathies are a family of related genetic syndromes resulting from gain-of-function mutations in genes involving the RAS/MAPK signaling pathway and include Noonan syndrome (OMIM #163950), Costello syndrome (OMIM #218040), Noonan syndrome with multiple lentigines (OMIM #151100), and cardiofaciocutaneous syndrome (OMIM #115050).¹ These syndromes have overlapping phenotypic features including skeletal, dermatologic, and neurocognitive findings. Cardiac phenotypes are also common, including valve stenosis or dysplasia, atrial and ventricular

septal defects, and hypertrophic cardiomyopathy (HCM).² More recently, the electrophysiologic phenotype has been described, with increased incidence of multifocal atrial tachycardia and EAT that occurred independent of HCM or valvular stenosis in 36% of patients and can be clinically challenging to control.³ It is theorized that calcium dysregulation results in triggered activity giving rise to the atrial tachycardia, as well as contributing to the cardiomyopathy phenotype.^{3,4}

The *SOS1* gene is located on chromosome 2p22 and encodes a guanine nucleotide exchange factor for RAS proteins. Gain-of-function mutations have been associated with Noonan syndrome, potentially accounting for up to 28% of cases.^{1,5,6} *SOS1*-mediated Noonan syndrome can have a mild phenotype, which may not be apparent until older ages when neurocognitive findings become more apparent, consistent with our presentation.^{6,7} Our patient was found to have a *de novo* missense mutation in a highly conserved amino acid residue of the pleckstrin homology domain–RAS exchanger motif domain linker that has not previously been reported. There was a single finding of this variant in the gnomAD dataset with the highest frequency 0.0024% (northwestern European). A similar missense variant affecting this residue (p.Leu550Pro, ClinVar VCV000040680) was shown to increase RAS exchange rates in vitro. Additionally, it has been reported in multiple individuals with Noonan syndrome and has been shown to cosegregate with disease within families.^{6,8,9}

Out-of-hospital cardiac arrest remains a rare entity in the pediatric population, though arrhythmias are common in the postarrest phase, likely owing to reperfusion, cytokine release, myocardial dysfunction, and associated catecholamine administration.^{10,11} While a variety of ectopy can be observed during this phase in pediatrics, incessant atrial tachycardia is atypical and is potentially more consistent with the arrhythmia phenotype seen in Noonan syndrome.¹⁰ Unexpected sudden death has also been reported in Noonan syndrome and is presumed to be due to ventricular arrhythmias in the setting of HCM and pulmonary stenosis.¹² To the extent of our knowledge, our case is the first reported ventricular fibrillation arrest associated with a RASopathy in the absence of the typical structural cardiac phenotypes of HCM or pulmonary stenosis. In fact, complex ventricular arrhythmias were previously rarely reported in these syndromes and not with documented cardiac arrest. Recently, Aly et al reported a case of neonatal Noonan syndrome with pulmonary valve stenosis, monocytosis, myeloproliferative disorder, and accelerated idioventricular rhythm resulting in severe hemodynamic compromise and ultimately contributing to patient demise.¹³ The accelerated idioventricular rhythm occurred following intervention to attempt right ventricular decompression and required extracorporeal membrane oxygenation support. Ultimately the rhythm was unable to be controlled and contributed to patient demise. This was the first reported complex ventricular arrhythmia affecting patient survival in *RIT1* variant-mediated Noonan syndrome. Our patient, however, did not have the cardiac manifestations of pulmonary valve

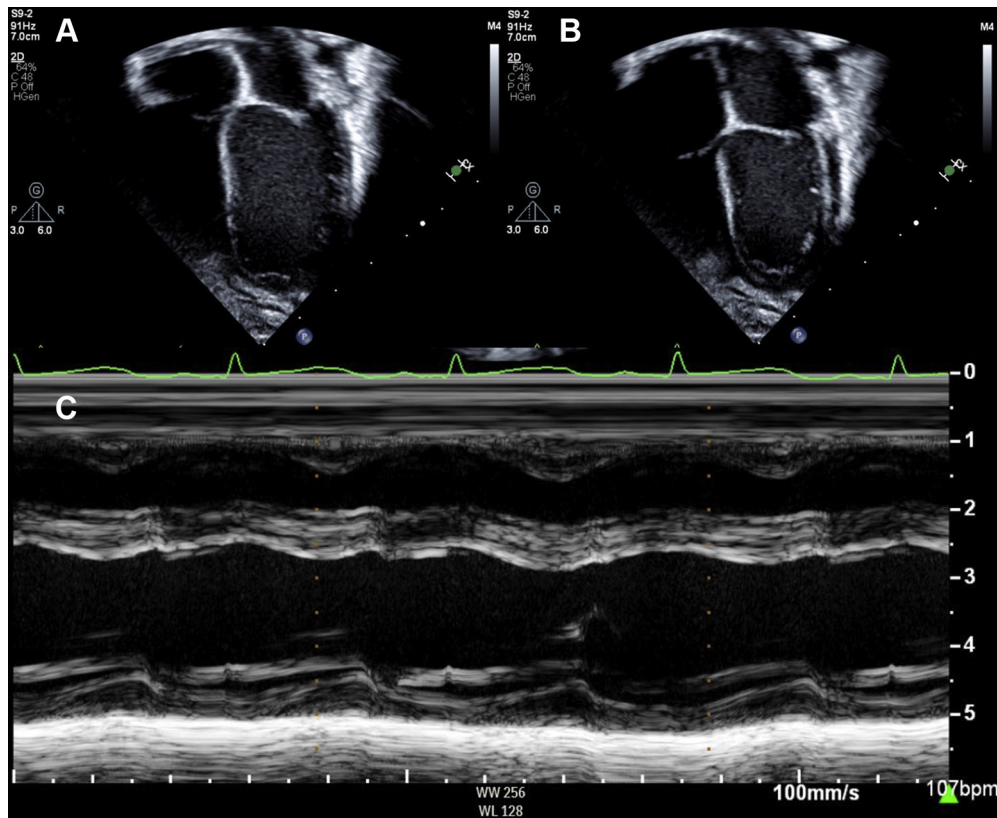


Figure 3 Apical 4-chamber view at (A) end diastole and (B) end systole at initial presentation. M-mode from (C) parasternal short axis view at presentation. Ejection fraction was 48.7% and shortening fraction 24.8%, which improved to 63.3% and 38.5%, respectively, at 1 month. There was normal valve morphology and function without evidence of ventricular hypertrophy, dilation, or noncompaction.

stenosis or history of intervention associated with her arrhythmia.

The limitation to this case report is the lack of definitive association of the *SOS1* variant with the presentation. In vitro studies have not been performed to confirm gain-of-function effects for this variant; however, comparison to similar variants is supportive. As this is a *de novo* variant in the family that has not previously been described, we are also unable to demonstrate cosegregation with disease. Our patient does not have typical features of Noonan syndrome at this time; however, the milder phenotype of *SOS1*-associated disease may become apparent over time and confirm this variant is putative for Noonan syndrome. She does demonstrate the arrhythmia phenotype of nonreentrant atrial tachycardia associated with RASopathies, which has been shown to manifest independently of other characteristic findings.³ Potentially this variant will be further clarified over time as additional carriers are reported.

Conclusion

We report the first case of a ventricular fibrillation arrest in a female infant with an *SOS1* variant in the absence of structural cardiac manifestations. This may represent a previously unrecognized etiology of unexpected sudden cardiac death in infants presumed healthy. Additionally, it supports the theory of ventricular arrhythmias as likely etiology of unexpected sudden death in patients with RASopathies.

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