

Expanding the electrical phenotype of *NKX2-5* mutations: Ventricular tachycardia, atrial fibrillation, and complete heart block within one family



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Introduction

NKX2-5 is a cardiac homeobox gene that is pivotal in the development of the myocardium and conduction system.¹ Cardiac structural abnormalities and conduction disturbances have been described in the pediatric population with *NKX2-5* mutations in recent years.² Of the structural abnormalities, atrial septal defect (ASD) is the signature phenotype, although conotruncal defects, systemic and pulmonary outflow obstructions, and cardiomyopathies have also been reported.^{3,4} Additionally, sudden death has been reported in patients with these mutations.⁵

Adult literature has demonstrated the presence of *NKX2-5* mutations in patients with lone atrial fibrillation presenting in their early 40s.⁶ However, there are no current reports of patients with *NKX2-5* mutations presenting with atrial fibrillation in teenage years or young adulthood. A recent study described the presence of ventricular tachycardia found incidentally on a pacemaker check in a patient with a strong family history of sudden death and *NKX2-5* mutations.⁷

We previously published a paper describing a novel mutation in the *NKX2-5* gene in a family with a history of sudden death.⁸ Our initial report described 2 male siblings with familial *NKX2-5* mutation who had congenital heart defects, left ventricular noncompaction cardiomyopathy, and bradyarrhythmias as children. We now present an update on these 2 patients as young adults who went on to develop tachyarrhythmias prompting implantable cardioverter defibrillator (ICD) therapy, highlighting the importance of maintaining a high index of suspicion and considering increased surveillance for potentially dangerous rhythm abnormalities in this patient population.

Case reports

We describe 2 male siblings (patients 1 and 2) with congenital heart disease and a family history of sudden death during

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sleep in their father at age 29 years. His autopsy diagnosis showed possible “left ventricular noncompaction cardiomyopathy.” Both siblings and their father (postmortem) tested positive for *NKX2-5* mutation c.512insGC.

Case 1

Patient 1 was the proband who was diagnosed with valvular pulmonary stenosis and a secundum ASD in infancy. He underwent pulmonary valvotomy and surgical closure of the ASD at age 7 years without any complications. He was also found to have first-degree atrioventricular (AV) block and apical noncompaction cardiomyopathy of the left ventricle (LV) that remained unchanged over the subsequent years. His left ventricular function remained normal. At age 11 years, he had multiple episodes of syncope and underwent an electrophysiology study. He was found to have normal AV nodal conduction and no inducible arrhythmias. At age 22 years, he was found to have asymptomatic progression of his AV nodal disease with QRS widening from 110 to 130 ms, suspicious for infranodal AV block. He underwent placement of a dual-chamber pacemaker. Shortly after, he was found to have multiple episodes of atrial flutter and fibrillation on a routine pacemaker interrogation, accounting for 30% of his rhythm (Figure 1). He was treated with beta-blockers for rate control and antiplatelet therapy. At age 23 years, his pacemaker interrogation revealed multiple episodes of nonsustained ventricular tachycardia in addition to atrial fibrillation. He subsequently underwent placement of an ICD, given family history of sudden death and known mutation. At his last follow-up 3 months after placement of an ICD, he was asymptomatic, with no ICD discharges.

Case 2

Patient 2 was also diagnosed with a secundum ASD, first-degree AV block, and LV noncompaction cardiomyopathy shortly after birth. He underwent an uncomplicated surgical ASD closure and was followed, with stable electrocardiographic (Figure 2A) and echocardiographic findings until age 18 years, when asymptomatic complete heart block was noted on his outpatient electrocardiogram (Figure 2B). Given the progression of his AV nodal disease in the setting

KEY TEACHING POINTS

- Children and young adults with *NKX2-5* mutations can present with a varied spectrum of electrical phenotypes in addition to their structural phenotype.
- Bradyarrhythmias such as atrioventricular block and tachyarrhythmias such as atrial fibrillation and ventricular tachycardia can all coexist in patients with *NKX2-5* mutations and may manifest as early as teenage years. It is pertinent to have a high index of suspicion for such arrhythmias and maintain longitudinal follow-up for patients with known *NKX2-5* mutation.
- Given the risk of sudden death in this population, early intervention with pacemaker implantation and/or implantable cardioverter-defibrillator placement should be considered.

of his known mutation, he underwent dual-chamber pacemaker implantation. A few months later, his device interrogation revealed atrial fibrillation (Supplemental Figure). He was also found to have short runs of ventricular tachycardia on his outpatient Holter monitor (Figure 3). His echocardiogram continued to show normal biventricular systolic function. Beta-blockers and antiplatelet therapy were initiated. However, at age 21 years, he was found to have longer runs of nonsustained ventricular tachycardia at higher rates, despite medications. With this family history of sudden death, it was recommended that he undergo an upgrade of his pacemaker to an ICD. At his most recent follow-up 1 month after ICD placement, he had no ICD discharges.

Discussion

We present an unusual phenotype of familial *NKX2-5* mutation with coexistence of high-grade AV block, atrial fibrillation, and ventricular tachycardia in siblings with a family

history of sudden cardiac death. Although their initial phenotype was predominantly that of structural heart defects, on follow-up they developed worsening AV nodal conduction prompting pacemaker implantation, as well as tachyarrhythmias requiring ICD placement. Our report expands the conventional electrophysiological phenotype of patients with *NKX2-5* mutations and highlights the maintenance of long-term follow-up of these patients.

NKX2-5 gene mutations and their role in congenital heart disease have gained significant interest in the recent years.⁹ A wide variety of structural defects have been identified in patients with this mutation. In a recent paper on 608 patients with congenital heart disease, 4% of patients with secundum ASDs were found to have heterozygous mutations in the *NKX2-5* coding region.² Mutations in this gene were also found in patients with other conotruncal abnormalities and left-sided obstructive lesions. Goldmuntz and colleagues⁴ found a prevalence of this gene defect in 4% of nonsyndromic TOF patients.

Nkx-2.5 belongs to a family of homeobox proteins and is related to the tinman gene found in *Drosophila melanogaster*. It has been found to play in role in cardiac morphogenesis and looping via regulation of transcription factors.¹⁰ Mice with heterozygous *NKX2-5* mutations were found to have atrial septal dysmorphogenesis and prolongation of PR interval.¹¹ In another murine model, atrial-specific *NKX2-5* mutants died shortly after birth and were found to have hyperplasia of atrial working myocardium and conduction system. This study alluded to the mechanism of arrhythmias and AV block, by suggesting that Nkx-2.5 has a suppressive role in cardiomyocyte proliferation.¹ A presumed mechanism for atrial fibrillation in these patients can be formation and/or proliferation of pulmonary myocardium, which can yield to arrhythmogenic substrates.⁶ A downstream target of Nkx-2.5 is calreticulin. In transgenic mice with overexpression of calreticulin, arrhythmia, chamber dilation, and sudden death at 6 to 10 weeks of age were demonstrated.¹²

Sudden death can occur in patients with mutations in the *NKX2-5* gene and is one of the most alarming aspects of this phenotypic spectrum.^{5,7} Although our patients' father shared the same *NKX2-5* gene mutation, his cause of death

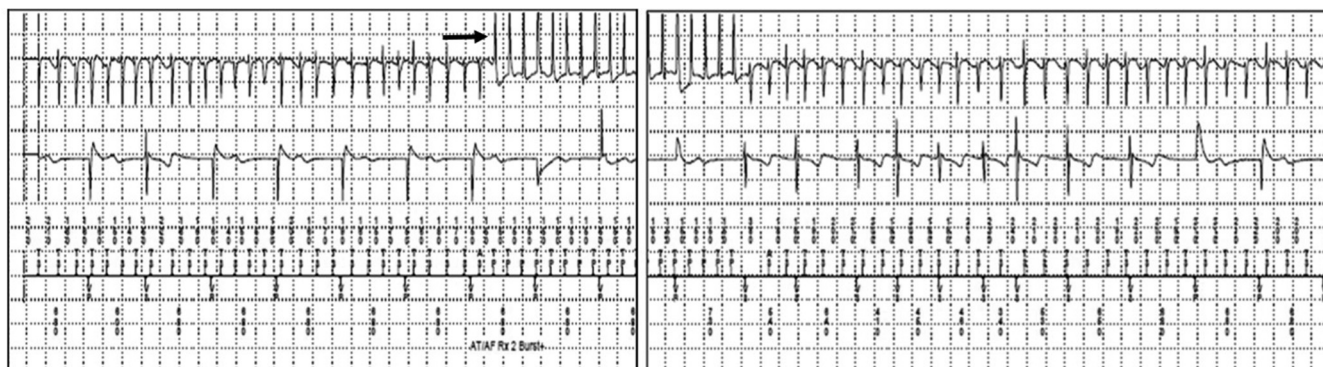


Figure 1 Pacemaker device interrogation for patient 1 showing atrial flutter at a cycle length of 160 ms, persistent despite antitachycardia pacing (arrow).

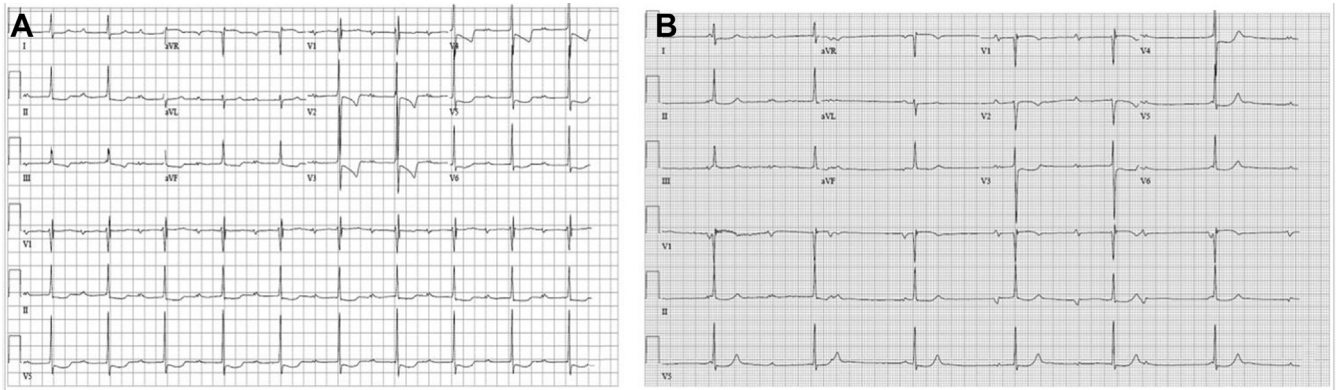


Figure 2 Progression of atrioventricular (AV) nodal disease in patient 2. **A:** Electrocardiogram (ECG) at 17 years showing sinus bradycardia and first-degree AV block with PR interval of 400 ms. **B:** ECG at 18 years showing complete heart block with AV dissociation and a narrow complex escape rhythm.

was unknown. Given the description of progressive AV block in these patients,¹³ we had presumed that he died of severe bradycardia in his sleep.⁸ However, in light of the tachyarrhythmias found subsequently in our patients in their older years, it is possible that the mechanism of death could have occurred from ventricular tachycardia or atrial fibrillation with rapid ventricular response.

In our review, we found that ventricular tachycardia has been sparsely described in patients with *NKX2-5* mutations. Perera and colleagues⁷ were the first to describe ventricular arrhythmia in *NKX2-5* mutations. This was present in 1 27-year-old patient among 11 family members with genotype- and phenotype-positive *NKX2-5* mutations. Of note, 2 of the patients in this family had sudden death despite functioning pacemakers placed for heart block. There were no family members in the study with atrial fibrillation. *NKX2-5* mutations have been found in adults in their 40s with lone atrial fibrillation.⁶ However, the presence of both tachyarrhythmias in patients in their early young adulthood has not been previously described. It should be noted that ventricular tachycardia can occur in as many as 17% of pediatric patients with LV noncompaction cardiomyopathy.¹⁴ The association of *NKX2-5* mutations and LV noncompaction cardiomyopathy has been described in recent literature,

particularly in mouse models.¹⁵ Whole exome sequencing was offered to the patients but was not performed owing to refusal. We postulate that given the inheritance pattern and clinical presentation of our patients, LV noncompaction and thus ventricular tachycardia is within the phenotypic spectrum of *NKX2-5* mutations.

Our updated findings shed light on the broad electrophysiological spectrum of *NKX2-5* mutations. It is important to note that conduction disturbances may coexist with tachyarrhythmias. Because our patients developed ventricular tachycardia in their young adulthood, we recommend maintaining a high index of suspicion with close monitoring. With the knowledge that sudden death has been described in these patients despite functioning pacemakers,⁷ we propose having a low threshold for placement of ICDs.

Conclusion

In conclusion, the current study expands the spectrum of *NKX2-5* mutations beyond conduction disturbances to potentially dangerous rhythm abnormalities that may develop over time. Whether ventricular tachycardia is a cause of sudden death in patients with *NKX2-5* mutations remains to be deciphered. Knowledge of these potential rhythm abnormalities



Figure 3 Holter monitor for patient 2 demonstrating a run of ventricular tachycardia at 180 beats/min.

is pertinent for early surveillance and prompt intervention in this patient population.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrcr.2018.08.001>.

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