Isolated Wolff-Parkinson-White syndrome in identical twins

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Introduction

Wolff-Parkinson-White (WPW) syndrome is a cause of paroxysmal supraventricular tachycardia and, occasionally, sudden cardiac death. Specific gene mutations in the *PRKAG2* gene have been linked to a subset of patients with familial WPW syndrome associated with cardiomyopathy.[1] Although the etiology of WPW syndrome is considered to be secondary to incomplete development of the atrioventricular septation, the mechanism and underlying genetic causes are relatively unknown. Additionally, no mutations have been identified in patients with the common form of isolated sporadic WPW syndrome.[2] It is not known whether accessory pathway formation is genetically determined, either by germline or somatic mutations, or is owing to random chance. We present male identical twins with WPW syndrome, without cardiomyopathy, both with similar pre-excitation pattern and accessory pathway location on the posterior mitral annulus.

Case report

Identical twin 1

A 28-year-old Korean-American patient was referred for palpitations during basketball practice sometimes associated with lightheadedness. A 12-lead electrocardiogram (ECG) showed sinus bradycardia at 44 beats per minute (bpm) with evidence of pre-excitation (Figure 1A). The patient underwent a transthoracic echocardiogram, which showed a left ventricular ejection fraction of 60%, normal left ventricular wall thickness, and normal right ventricular size and function, and no valvular pathology. The patient had normal routine baseline laboratory testing.

The patient underwent diagnostic electrophysiology (EP) study under conscious sedation. At baseline, the R-R interval was 1449 ms, PR 100 ms, QRS 127ms, QT 400 ms, AH 71 ms, and HV 28 ms. In the basal state, the anterograde accessory pathway Wenckebach cycle length was 380 ms, and the effective refractory period was <290 ms at a drive cycle of 600 ms. The retrograde Wenckebach cycle length of the accessory pathway was 360 ms. No tachycardia or echo beats were seen with atrial and ventricular pacing without and with isoproterenol. Mapping via a transseptal approach revealed that the accessory pathway was located on the posterior aspect of the mitral annulus (Figure 1C). Several applications of radiofrequency energy to the mitral annulus were performed and the third application resulted in elimination of accessory pathway conduction. He tolerated the procedure well. At follow-up office visit 3 months later, the 12-lead ECG showed sinus rhythm with J-point elevation and no evidence of pre-excitation. He had no further symptoms.

Identical twin 2

The 28-year-old brother of identical twin 1 was referred for palpitations, also while playing basketball, with subsequent lightheadedness lasting 30–45 seconds. A 12-lead ECG showed sinus bradycardia at 49 bpm and pre-excitation (Figure 1B). The transthoracic echocardiogram showed normal left ventricular ejection fraction of 60% without evidence of ventricular hypertrophy. The patient had normal routine baseline laboratory testing. The patient underwent diagnostic EP study under conscious sedation. At baseline, the R-R interval was 1210 ms, PR 110 ms, QRS 144 ms, QT 410 ms, AH 74 ms, and HV 10 ms. The accessory pathway anterograde effective refractory period was <290 ms with a drive cycle length of 600 ms. During ventricular pacing, there was evidence of eccentric atrial activation

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KEY TEACHING POINTS

- Wolff-Parkinson-White (WPW) syndrome with or without cardiomyopathy may be associated with a familial pattern of inheritance.
- Several genes have been identified in patients with familial WPW with associated cardiomyopathy, including mutations in the *PRKAG2* gene.
- However, the etiology of isolated sporadic WPW syndrome remains unknown.

with earliest activation on the posterior mitral annulus. No tachycardia or echo beats were seen with atrial and ventricular pacing without and with isoproterenol. A transseptal puncture was performed and a 3-dimensional mapping system (EnSite Velocity, St. Jude Medical, St. Paul, MN) without fluoroscopy was used to map both anterograde and retrograde pathway activation using a roving 4-mm-tip mapping and ablation catheter. The earliest activation was noted on the posterior mitral valve annulus (Figure 1D). The first radiofrequency application eliminated retrograde conduction after 2 seconds. At the end of the procedure, there was no evidence of pre-excitation and no evidence of ventriculoatrial conduction. At a follow-up visit 5 weeks later, the patient remained asymptomatic, with 12-lead ECG showing sinus bradycardia at 54 bpm with no evidence of pre-excitation or left ventricular hypertrophy.

The parents of the twins are both alive and well, without palpitations or cardiac history. Their family history is unremarkable, with no sudden cardiac death, pacemaker, heart failure, or cardiomyopathy. Their sister has a normal ECG and no cardiac symptoms. Neither twin had offspring.

Whole exome sequencing was performed on identical twin 2 using the Agilent SureSelect V5 (Agilent Technologies, Santa Clara, CA) plus a mitochondrial analysis. Exome and mitochondrial sequencing libraries were run on the Illumina HiSeq 2500 (Illumina Inc, San Diego, CA) using 100 base pair paired-end reads to an average depth of coverage of 85–100×. Minimum read depth for analysis was 10× coverage. Sequences were aligned on the human genome build GRCH37/UCSC hg19 using a custom bioinformatics analysis pipeline. Variants were annotated using Cartagenia Bench software (Agilent Technologies) following American College of Medical Genetics guidelines.[3] There were no pathogenic gene mutations identified. Whole exome sequencing was offered to first-degree relatives, but the family declined.

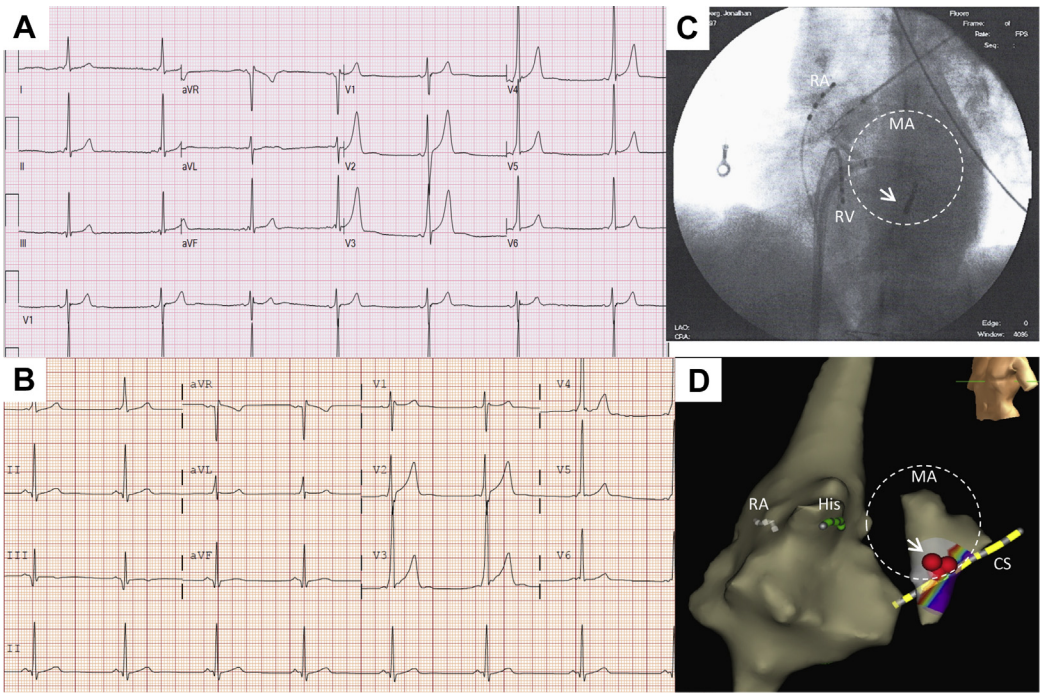

Figure 1 **A:** Presenting electrocardiogram from identical twin 1 is shown. **B:** Presenting electrocardiogram from identical twin 2 is shown. Note there is pre-excitation with a similar pattern of pre-excitation among the twins. **C:** Successful ablation site of accessory pathway in identical twin 1 is shown in this left anterior oblique fluoroscopic image. The ablation catheter (*arrow*) is at the successful site of accessory pathway ablation along the posterior mitral annulus. **D:** Successful ablation site of accessory pathway in identical twin 2 is shown in this left anterior oblique 3-dimensional mapping system image (EnSite Velocity, St. Jude Medical). Successful ablation site (*arrow*) is shown in a similar location along the posterior mitral annulus, with red markers representing radiofrequency lesions. An octapolar catheter in the proximal coronary sinus is shown in yellow, a quadripolar catheter at the His bundle location is shown in green, and a quadripolar catheter at the right atrium is shown in white. In both C and D, dashed circle represents the approximate location of the mitral annulus. CS = coronary sinus; His = His bundle; MA = mitral annulus; RA = right atrium; RV = right ventricle.

Discussion

WPW syndrome has long been known to occasionally occur in an inherited manner.[2,4–6] In the series by Vidaillet and colleagues,[6] accessory pathways were documented in 1 or more first-degree relatives of 13 of 383 (3.4%) patients with WPW syndrome. The *PRKAG2* gene has been shown to be associated with WPW syndrome in an autosomal dominant pattern associated with heart disease such as hypertrophic cardiomyopathy.[1] Several other rare genetic syndromes may be associated with pre-excitation and are summarized in a review by Koneru and colleagues.[7]

Unlike the WPW syndrome associated with structural cardiac disease or systemic disease, the molecular and genetic basis of the more common isolated sporadic WPW syndrome and accessory pathway formation is unknown.[2] Population studies assessing patients with isolated WPW syndrome for mutations in candidate genes, such as *PRKAG2*, have not demonstrated any associated mutations.[8] However, retrospective studies of sporadic WPW syndrome have demonstrated a relationship between racial background and accessory pathway location, suggesting an inherited component to accessory pathway development.[9]

Relevant to the current case, a separate report identified a mother and her son both with manifest right free wall accessory pathways in identical anatomic locations.[10] In terms of previously published case reports in twins, Lu and colleagues[11] described identical twins who both had left lateral accessory pathways in the same location of the mitral valve annulus, but 1 of the twins did not have pre-excitation on 12-lead ECG and the concealed accessory pathway was discovered at EP study. In older reports, 1 from the 1950s and 2 from the 1970s, the location of the accessory pathway has varied between twins,[12] or only 1 of the 2 twins had evidence of atrioventricular pre-excitation while the other was described as having Lown-Ganong-Levine syndrome with a short PR but no evidence of atrioventricular pre-excitation.[13,14]

The mechanism resulting in the presence of accessory pathways is unknown. It may be determined by mosaic somatic mutations or environmental exposure, or may simply represent random events during embryonic heart development causing failed fusion of the AV junctional tissues, resulting in persistent connections at the margins of the atrioventricular node.[2] A number of candidate genes proposed include transcription factors involved in the development of the atrioventricular ring and the cardiac conduction tissue.[2]

While no pathogenic mutations were identified in the current set of identical twins, 1 of whom underwent whole genome sequencing, the fact that the twins both developed the accessory pathway with identical anatomic location suggests that there was a germline mutation rather than a random event during later embryonic heart development. Further investigations using functional studies or functional modeling of known variants, whole genome sequencing, or epigenetic studies may better elucidate the etiology of accessory pathway development in sporadic WPW syndrome.

Conclusion

Here we report a case of identical twins both presenting with WPW syndrome with manifest accessory pathways in a similar location on the posterior mitral valve annulus. The finding supports that the pathogenesis of some forms of "lone" WPW syndrome (occurring in the absence of a cardiomyopathy) has a genetic etiology that has yet to be elucidated.

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