Unusually High Association of Hypertrophic Cardiomyopathy and Complex Heart Defects in Children with Fasciculoventricular Pathways

SUDHIR VASHIST, M.D.,* JENNIFER N.A. SILVA, M.D.,* GEORGE F. VAN HARE, M.D.,*
ANDREW L. PAPEZ, M.D.,† WILBER W. SU, M.D.,‡ and EDWARD K. RHEE, M.D.§

From the *Department of Pediatric Cardiology, Washington University School of Medicine/St. Louis Children's Hospital, St. Louis, Missouri; †Phoenix Children's Hospital & Arizona Pediatric Cardiology Consultants/Pediatrix, Phoenix, Arizona; ‡St. Joseph's Hospital and Medical Center, Phoenix, Arizona; and §Eller Congenital Heart Center, Heart Lung Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

Introduction: Fasciculoventricular pathways (FVPs) are rare causes of preexcitation that do not mediate tachycardias. We report a two-center experience of pediatric patients with FVP and an unexpectedly high association of complex congenital heart defects (CHDs), chromosomal anomalies, and hypertrophic cardiomyopathy.

Methods: A retrospective review of the electrophysiology database at two institutions was performed to identify patients with FVP from January 2000 to January 2011. Medical records of these patients were reviewed for clinical history and course, presence of comorbidities, and details of intracardiac electrophysiology (EP) study.

Results: A total of 17 patients were identified. The primary indication for EP study was a preexcitation pattern on electrocardiogram. The majority of patients, 12/17 (71%), were found to have associated cardiac and genetic anomalies. Hypertrophic cardiomyopathy was found in 5/17 (29%) patients, with genetic testing in two patients demonstrating the lysosomal-associated membrane protein 2 mutation (Danon syndrome). Underlying complex CHDs were present in 3/17 (18%) patients. One patient (6%) was status post (s/p) cardiac transplant, one patient had hypertension, and another had Trisomy 21. Other electrophysiologic substrates mediating tachycardia were found in 3/17 (18%) patients. Only 5/17 patients (29%) were otherwise healthy with structurally normal hearts.

Conclusions: In this largest reported series of FVP in children, there is an unusually high association of FVP with complex CHDs, chromosomal anomalies, and hypertrophic cardiomyopathy. Any patient with such disorders and manifest preexcitation should be evaluated with a high index of suspicion for a FVP. (PACE 2012; 35:308–313)

electrophysiology—clinical, ***electrocardiogram***, ***pediatrics***, ***SVT***

Introduction

Wolff-Parkinson-White (WPW) syndrome is the most common cause of ventricular preexcitation, accounting for >95% of cases; however, preexcitation can also be mediated by atypical bypass tracts such as nodoventricular, nodofascicular, slowly conducting atrioventricular, atriofascicular, and fasciculoventricular connections. Accessory pathways associated with WPW have nondecremental antegrade and retrograde conduction and are mostly associated with orthodromic atrioventricular reentrant tachycardia (AVRT). In contrast, atypical bypass tracts typically conduct in an antegrade decremental fashion, and can either mediate antidromic AVRT or act as innocent bystanders during other supraventricular tachycardias (SVT). The arrhythmias mediated by the atypical bypass tracts manifest as wide-complex tachycardias with a left bundle branch block (LBBB) morphology, making them difficult to differentiate from some ventricular tachycardias. This is particularly true in the case of nodoventricular and nodofascicular fibers that can mediate antidromic AVRT with atrioventricular (AV) dissociation.

Among these unusual forms of preexcitation, fasciculoventricular pathways (FVPs) are the rarest[1] and are not capable of mediating tachyarrhythmias.[1–6] Of those patients undergoing electrophysiologic study (EPS), the incidence of FVP in patients with preexcitation on surface electrocardiogram (ECG) is 1.8%–9.8%.[2,5,6] Both noninvasive and invasive electrophysiologic attributes of FVP have been well characterized.[4,7]

On the surface 12-lead ECG, there is a preexcited QRS with a normal PR interval. During EPS, His bundle recordings show a normal atrial-His (AH) bundle and short His-ventricular (HV) bundle interval at baseline, and with atrial overdrive pacing or atrial extrastimulation (AES) testing, there is progressive AH prolongation with a stable HV interval and QRS morphology. This is in contrast to other atypical variants of preexcitation where with progressively shorter atrial pacing cycle lengths or AES coupling intervals, A-delta interval increases, the QRS gets wider, and the HV interval decreases with His potentials progressively inscribed within the QRS and eventually activated retrogradely.

Most case reports describe FVPs as an isolated electrophysiologic abnormality of no clinical consequence and with no cardiac or extracardiac associations. Case reports have described patients with FVP in conjunction with other arrhythmia substrates, such as accessory pathways (both manifest and concealed)[2,5,8,9] and AV nodal reentrant tachycardia.[7,10,11] Also, case reports of patients with FVP have been reported in association with hypertrophic cardiomyopathy (HCM),[3,8] atrial septal defect (ASD),[8] and ventricular septal defect (VSD).[5,8] Recently, a series[12] of mostly adult patients with PRKAG2 mutation associated glycogen storage cardiomyopathy has also been reported in association with FVP.

This case series describes the pediatric experience from two centers of patients with FVP and an unusually high association with complex congenital heart defects (CHDs), chromosomal anomalies, and inherited cardiomyopathies.

Methods

Patient Population

After obtaining approval of the Institutional Review Boards at Washington University (St. Louis, Missouri) and St. Joseph's Hospital and Medical Center (Phoenix, Arizona), a retrospective review of the electrophysiology database was undertaken to identify patients with the diagnosis of FVP from January 2000 through January 2010. Data were collected from the medical record and the EP recording system (Prucka Engineering, GE Medical, Wauwatosa, WI, USA). All patients with FVP were included in the study; there were no exclusionary criteria.

Electrophysiologic Data

Baseline 12-lead electrocardiograms were analyzed for the evidence of preexcitation, QRS duration, and PR interval. Electrophysiologic studies recorded on a conventional EP recording system were reviewed. Measured PR intervals were compared with the normal age-adjusted PR intervals published in the literature.[13] The AH interval was measured from the onset of local atrial activation (defined as earliest reproducible rapid deflection of the atrial electrogram) on the His bundle electrode catheter to the onset of His deflection (defined by the earliest His deflection from the baseline). The HV interval was measured from the beginning of the His bundle deflection on the His bundle electrode catheter to the earliest onset of ventricular activation in any intracardiac or surface ECG lead. These measured intervals were compared to the normal range of AH and HV intervals of 50–120 ms and 25–50 ms, respectively, published in the literature for pediatric patients.[14]

Pacing maneuvers were performed to establish a diagnosis of FVP and rule out other forms of preexcitation. Incremental atrial pacing along and AES testing was performed from coronary sinus and right atrium.

The diagnosis of FVP was made if the following characteristics were present:

(1) A preexcited QRS in the surface ECG with normal PR interval.
(2) Baseline intervals: normal AH and short HV.
(3) During AES testing or atrial burst pacing: prolongation of AH interval with unchanged HV interval and QRS morphology (see Fig. 1).

In addition, no change in preexcitation along with unchanged HV interval with junctional beats when present was also supportive of the diagnosis (see Fig. 2). Junctional beats with persistent preexcitation imply the source of preexcitation distal to the His bundle consistent with FVP. In all other variants of preexcitation, junctional beats would manifest with narrow QRS due to the loss of preexcitation and normalization or prolongation of the HV interval.

Demographic and Clinical Data

Medical records of these patients were reviewed for clinical presentation, indication of the EPS, and clinical course. The presence of associated structural and genetic cardiac defects as well as other comorbidities was examined.
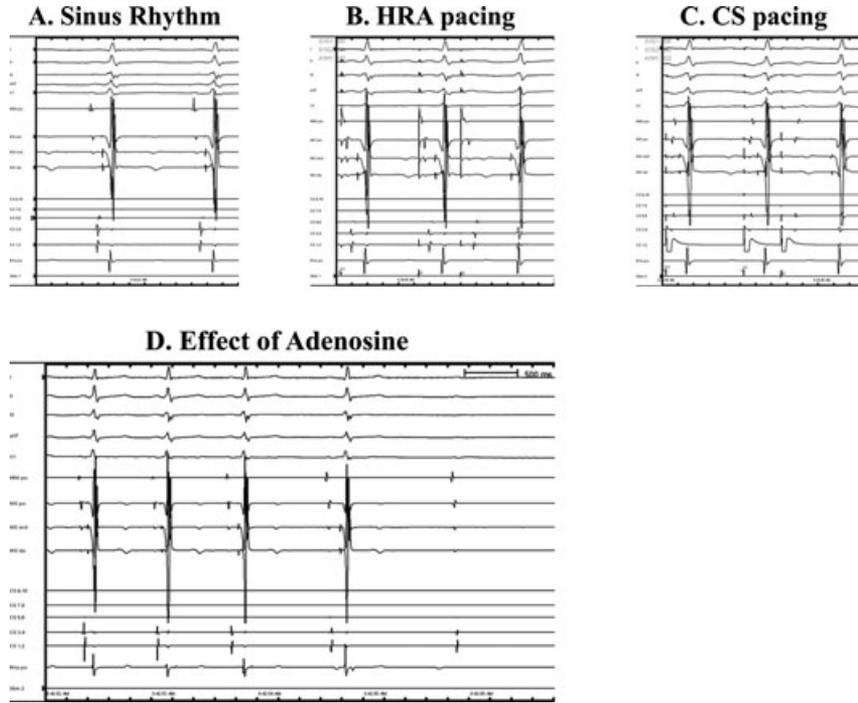
Statistics

Descriptive statistics are expressed as median (with range) and percentages.

Results

Baseline Data

A total of 17 patients with FVP were identified (see Table I). The median age was 13 years (range 1–24 years). Twelve of 17 patients (71%) were

Figure 1. *Tracings obtained from intracardiac electrophysiologic study (EPS) from a patient with fasciculoventricular pathway (FVP). Panel A demonstrates preexcited sinus rhythm. Panels B and C demonstrate no change in preexcitation with high right atrium or coronary sinus pacing respectively. Panel D shows the effect of adenosine in the same patient with progressive AH prolongation leading to complete AV block with constant HV interval and no change in QRS morphology. Earliest ventricular depolarization is on the His bundle catheter.*
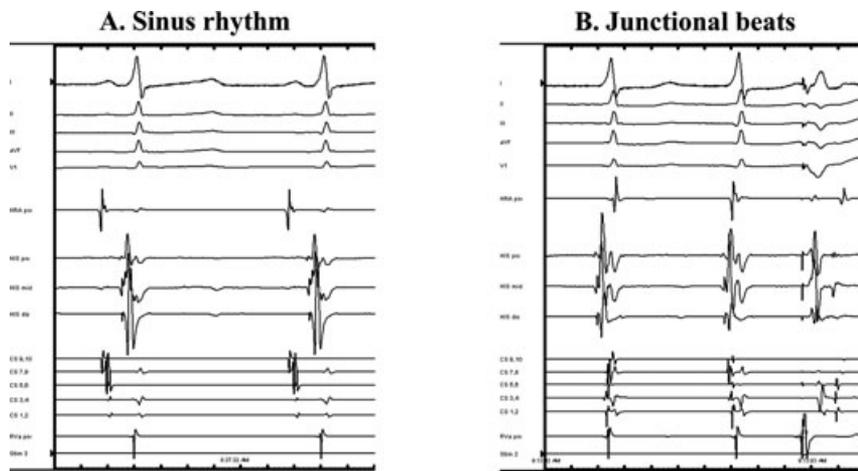
Figure 2. *This is an example of a patient with spontaneous junctional beats. Panel A shows baseline preexcited sinus rhythm. Panel B demonstrates no change in preexcitation with spontaneous junctional beats in the same patient. Earliest ventricular depolarization is again seen on the His bundle catheter.*

Table I.

Patient Demographic and Clinical Data

Patient	Age (years)	Gender	Associated Diagnoses	Electrophysiologic Diagnosis
1	15.8	M	Hypertrophic cardiomyopathy (LAMP2 mutation)	FVP multifocal atrial tachycardia right free wall accessory pathway
2	17.7	M	Hypertrophic cardiomyopathy (LAMP2 mutation)	FVP
3	24.4	M	Hypertrophic cardiomyopathy	FVP right free wall accessory pathway
4	18.7	M	Hypertrophic cardiomyopathy	FVP
5	13.1	F	Hypertrophic cardiomyopathy	FVP
6	2.5	M	Double outlet right ventricle mitral atresia, {S,L,L}	FVP
7	8.5	M	Tetralogy of Fallot s/p repair Trisomy 21	FVP
8	1.1	F	Pulmonary atresia/intact ventricular septum s/p OHT	FVP
9	4.3	F	Tricuspid atresia s/p glenn	FVP
10	6.5	M	Trisomy 21	FVP
11	16.4	F	Essential hypertension	FVP
12	11.3	M	WPW	FVP multiple right free wall accessory pathways
13	16	M	Healthy	FVP
14	12	M	Healthy	FVP
15	11.1	M	Healthy	FVP
16	16	M	Healthy	FVP
17	18.4	F	Healthy	FVP

LAMP2 = lysosomal-associated membrane protein 2; FVP = fasciculoventricular pathway.

male. In all 17 patients, the primary indication for EPS was a preexcitation pattern on the ECG suspicious for WPW syndrome. In addition, 14/17 (82%) patients had complaints of chest pain, palpitation or syncope, abnormal Holter, or an abnormal event monitor tracing.

Associated Cardiac/Genetic Anomalies

Twelve of 17 patients (71%) were found to have an associated cardiac or genetic anomaly. HCM was identified in 5/17 (29%) patients. Two of these patients underwent genetic testing and were found to have a lysosomal-associated membrane protein 2 (LAMP2) mutation, consistent with Danon syndrome, a form of hereditary HCM. These two patients were not related to each other. Two patients with HCM did not undergo genetic testing and the results of genetic testing were pending in one. Underlying complex CHD (see Table I) was found in 3/17 (18%) patients, including tetralogy of Fallot, double outlet right ventricle, and Tricuspid Atresia. One patient (6%) was s/p cardiac transplant (OHT) for pulmonary atresia/intact ventricular septum at the time of EPS. Isolated essential hypertension was seen in one patient, and another had Trisomy 21.

Three patients were noted to have tachycardia-mediating electrophysiologic substrates in addition to the FVP. In all three of these patients, the arrhythmias were clinically expressed. One patient presented to the emergency room (ER) with palpitations and 12-Lead ECG demonstrated SVT. He was found to have multiple right free wall accessory pathways (one manifest, one concealed) and underwent successful ablation. A patient with Danon disease had a single right free wall concealed accessory pathway in addition to multifocal atrial tachycardia (MAT). He also presented to the ER with palpitations on two occasions, once for MAT and an other time for AVRT related to concealed accessory pathway. He underwent successful ablation of the accessory pathway. Another patient with HCM s/p implantable cardioverter defibrillator underwent successful ablation of concealed right lateral accessory pathway. No patients in this cohort were found to have other variants of preexcitation. Only 5/17 (29%) of the patients were otherwise healthy with no associated cardiac or genetic anomalies.

Discussion

In this case series of FVP in pediatric patients, the largest published to date, an unusually high association of FVP with complex structural heart defects, HCM, and chromosomal anomalies is reported. In fact, 12/17 (71%) of the patients reported had associated cardiac or genetic anomalies. Additionally, 3/17 (18%) of the patients were noted to have other electrophysiologic substrates besides FVP that were capable of mediating tachycardia.

The current pediatric literature on FVP[5,8] remains sparse. In a series of three patients reported by Sallee and Van Hare,[5] only one patient was reported with Trisomy 21 and a VSD (which closed spontaneously). In another series reported by Ratnasamy et al.,[8] 2/12 (16.6%) patients had simple structural heart defects (such as ASD and VSD) in association with FVP. Rarely, FVPs have been reported as an incidental finding in patients with other arrhythmia substrates, such as AVNRT,[7,10,11] WPW,[9] or concealed accessory pathway.[2,5,8,9] In the cohort reported above, 3/17 (18%) patients with FVP also had other tachycardia-mediating electrophysiologic substrates. One patient had two right free wall accessory pathways (one manifest and one concealed), the second patient had right free wall concealed accessory pathway in addition to MAT, and the third patient had concealed right lateral accessory pathway.

Five of 17 patients (29%) in this series were diagnosed with HCM, an unusually high percentage given that this has been reported infrequently previously in the literature.[3,8,12] Interestingly, two of these five patients in this cohort had LAMP2 mutation consistent with Danon disease as the cause of their HCM. Danon disease, a rare X-linked genetic disorder due to deficiency of LAMP2, results in secondary intracytoplasmic glycogen storage. Clinical features include early-onset HCM, preexcitation on ECG, variable degrees of muscular weakness, mental retardation, and retinal changes. There are few documented cases of Danon disease with manifest accessory pathway mediated tachycardia requiring ablation.[15]

It has been postulated that a WPW pattern in glycogen storage diseases such as PRKAG2 mutation-associated cardiomyopathy, Danon, Pompe's, and Fabry's could be due to bypass tracts, enhanced AV nodal conduction,[16] fasciculoventricular connections,[12] or ventricular conduction disease.[17,18] A recent study[19] using a mouse model of the PRKAG2 mutation as the prototype of glycogen-storage cardiomyopathy identified annular disruption adjacent to the anterior septum by glycogen-engorged myocytes as the cause of preexcitation rather than true presence of a morphologically distinct bypass tract as the substrate for ventricular preexcitation. The authors postulated this to be the possible mechanism of preexcitation in other glycogen-storage disorders such as Danon disease. If the glycogen-engorged myocytes disrupt His bundle insulation by similar mechanism, this supports the hypothesis proposed by Sallee and Van Hare[5] that FVPs are a disruption of His bundle insulation rather than true bypass fiber connection. In a separate study[20] published in the Journal of the American College of Cardiology (JACC) by the same group involving the same animal model of PRKAG2 mutation, serial ECG recordings in newborn transgenic mice demonstrated development of preexcitation with age. Although no transgenic mice had preexcitation at birth, 25% demonstrated preexcitation after first postnatal week, and 88% showed preexcitation by 4 weeks of life. The authors hypothesized that accessory AV connections are induced in postnatal life after completion of cardiac organogenesis. Also cardiac myocytes may alter their conductive properties related to water accumulation and alteration of ionic environment as a result of intracellular glycogen accumulation. This may promote accelerated conductance and disruption of annulus fibrosis leading to the development of preexcitation over a period of time. All the patients in our study had evidence of preexcitation on the initial ECG; as such we could not establish if the preexcitation was acquired with age. Although there are reports[12,21] of patients with PRKAG2 mutation-associated cardiomyopathy and FVP suggesting more widespread involvement of this mutation in cardiac conduction system development, to the best of our knowledge, there are no reported cases of FVP in association with Danon disease.

Study Limitations

A limitation of this study is selection bias, as most patients were enrolled at a referral center for heart failure and cardiac transplant, which may have spuriously elevated the number of patients with complex diagnosis, including cardiomyopathies. Also, given that this study is a retrospective chart review, there may be recall bias.

Conclusion

In conclusion, this is the largest report on pediatric FVP to date, and the first to report the unusually high association of complex structural heart defects, HCM, and chromosomal anomalies in association with FVP. Careful evaluation for FVP as a cause of preexcitation should be sought while evaluating such patients for preexcitation pattern on the ECG.

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