Brief Report

Association of Wolff-Parkinson-White With Left Ventricular Noncompaction Cardiomyopathy in Children

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ABSTRACT

Background: Wolff-Parkinson-White (WPW) has been associated with left ventricular noncompaction (LVNC) in children. Little is known about the prevalence of this association, clinical outcomes, and treatment options.

Methods: Retrospective review of subjects with LVNC. LVNC was defined by established criteria; those with congenital heart disease were excluded. Electrocardiograms (ECGs) were reviewed for presence of pre-excitation. Outcomes were compared between those with isolated LVNC and those with WPW and LVNC.

Results: A total of 348 patients with LVNC were identified. Thirty-eight (11%) were found to have WPW pattern on ECG, and 84% of those with WPW and LVNC had cardiac dysfunction. In Kaplan−Meier analysis, there was significantly lower freedom from significant dysfunction (ejection fraction $\leq$ 40%) among those with WPW and LVNC ($P < .001$). Further analysis showed a higher risk of developing significant dysfunction in patients with WPW and LVNC versus LVNC alone (hazard ratio 4.64 [2.79, 9.90]). Twelve patients underwent an ablation procedure with an acute success rate of 83%. Four patients with cardiac dysfunction were successfully ablated, 3 having improvement in function.

Conclusion: WPW is common among children with LVNC and is associated with cardiac dysfunction. Ablation therapy can be safely and effectively performed and may result in improvement in function. (*J Cardiac Fail 2019;25:1004−1008*)

Key Words: Arrhythmia, cardiomyopathy, pediatrics, trabeculation.

Left ventricular noncompaction (LVNC) is a form of cardiomyopathy characterized by deep trabeculations within the left ventricle.[1,2] It has been associated with a high risk of cardiac events in children including cardiac dysfunction, arrhythmias, and sudden death.[3,4] One association that has been reported with LVNC is Wolff-Parkinson-White (WPW), with previous estimated incidences of 5% to 17%.[4−8] However, the overall prevalence, characteristics, and outcomes of this group remain poorly understood.

We conducted a single-center retrospective evaluation of children with WPW and LVNC to assess clinical characteristics, treatment, and outcomes in this population. This cohort was compared with those with LVNC without WPW to test the hypothesis that WPW was a risk factor for increased morbidity and mortality.

Methods

The study was IRB approved, and individual consent was waived. The institutional database was searched for children with the diagnosis of LVNC or prominent trabeculations between 1990 and 2017. Clinical documents and echocardiograms were reviewed to ensure that the patients met criteria for LVNC based on documented diagnosis or the Jenni criteria.[2] Patients with associated congenital heart disease were excluded. For remaining patients, electrocardiograms were examined for the presence of ventricular pre-excitation, consistent with WPW(JK). Medical records

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See page 1007 for disclosure information.

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were reviewed to document demographics, clinical course, and outcomes. In addition, all patients had serial echocardiography analyzed for measures of systolic function. Cardiac dysfunction was defined as an ejection fraction (EF) of <55% (Simpson's or bullet method) or shortening fraction (SF) less than −2 z scores for age. Qualitative assessment of ventricular dyssynchrony was also collected. Phenotypes were assigned based on published criteria.[2,9]

Statistical Analysis

Continuous variables were presented as medians with interquartile range (IQR). Wilcoxon rank sum test was applied to compare data distribution between the 2 patient groups. Categorical variables were tabulated as counts with percentages and proportions compared using Fisher's exact test. Survival analyses were evaluated by the Kaplan−Meier estimator and log rank test. To account for different follow-up times, univariate and multivariable Cox regression models were used to evaluate risk factors associated with time to cardiac dysfunction. For survival analyses and Cox regression models, patients were censored at last documented clinical follow-up. For inclusion into the multivariable Cox regression model, a *P*value of <.2 was used with subsequent stepwise backward elimination. Dyssynchrony was removed from the model as it is on the causal pathway. To appropriately model phenotypes as a predictor for cardiac dysfunction, a time-dependent covariate method was used. The proportional hazards assumption was not met for sex and therefore a log rank *P*value was used for completeness in the univariate model. Interaction testing showed no interaction between WPW and sex and therefore it was not included in the multivariable model. SAS v9.4 (SAS Institute Inc, Cary, NC) was used for analysis.

Results

Study Population Demographics

In total, 348 patients with LVNC met entry criteria for analysis. Of these, 223 (64%) were male and 125 (36%) were female. The median age at diagnosis was 6.8 years (IQR 0.51, 13.75) and 113 (32%) were infants. Of the 348 patients with LVNC, 38 (11%), were noted to have preexcitation consistent with WPW on EKG. The demographics for patients with coexistent WPW and LVNC compared with LVNC without WPW can be seen in Table 1.

Phenotype Associations and Cardiac Function

As shown in Table 1, 45% of patients within the WPW and LVNC group had a dilated phenotype compared with 24% of those with LVNC without WPW (*P*= .047). The majority of patients with WPW and LVNC, 32 (84%) had cardiac dysfunction as defined as an LV EF <55% or SF of < −2 z scores compared with 52% in those without WPW. Only 1 case of dysfunction within the WPW group was potentially linked with supraventricular tachycardia (SVT).

Table 1. Patient Demographics, Characteristics, and Outcomes by WPW

Parameter	WPW+LVNC (N=38)	LVNC Without WPW (N=310)	*P* Value
Median age at diagnosis, years (IQR)	3.4 (0.3, 12.6)	6.8 (0.6, 13.8)	.238
Age at diagnosis, years			
<1	18 (47.4)	95 (30.6)	.093
1−11	8 (21.1)	109 (35.2)	
≥12	12 (31.6)	106 (34.2)	
Sex, N (%)			
Female	17 (44.7)	108 (34.8)	.282
Male	21 (55.3)	202 (65.2)	
Race/ethnicity, N (%)			
White	13 (34.2)	78 (25.2)	.546
Black	14 (36.8)	141 (45.5)	
Hispanic	11 (28.9)	72 (23.2)	
Asian	0	9 (2.9)	
Other	0	1 (0.3)	
Unknown	0	9 (2.9)	
Phenotype, N (%)			
Isolated	11 (28.9)	143 (46.1)	.047
Dilated	17 (44.7)	73 (23.5)	
Hypertrophied	5 (13.2)	61 (19.7)	
Mixed	5 (13.2)	33 (10.6)	
Median follow-up time, (IQR)	4.74 (1.81,7.14)	3.07 (0.47, 7.74)	.091
SVT, N (%)	17 (44.7)	10 (3.2)	***
Dyssynchronous contraction, N (%)	18 (47.4)	61 (19.7)	***
Cardiac dysfunction, N (%)*	32 (84.2)	161 (51.9)	***
Heart transplant, N (%)	2 (5.3)	22 (7.1)	***
Death, N (%)	6 (15.8)	25 (81)	***
Cardiac death (heart transplant or death), N (%)	8, (21.1)	43 (13.9)	***
Sudden death, N (%)	1 (2.7)	6 (1.9)	***

*Cardiac dysfunction is defined as EF < 55% or Shortening Fraction <−2 z score.

****P* values not reported because of clinically disparate times of follow-up. All follow-up times were accounted for in subsequent analysis when meeting proportional hazards.

The majority of patients, in both groups, with dysfunction had it at time of presentation (75% in WPW and LVNC and 83% in LVNC alone). In patients who did not present with dysfunction, a Kaplan−Meier (KM) analysis was performed to evaluate the risk of development of dysfunction between patients with WPW and LVNC versus LVNC alone. As shown in Fig. 1a, there was significantly lower freedom from cardiac dysfunction in those with WPW (*P*< .001). Additional analyses were completed to determine whether WPW was a risk factor for the development of significant dysfunction (EF ≤ 40%). This analysis was limited to the 83% of patients who had functional assessment completed using EF (87% within WPW cohort and 82% within LVNC alone cohort). On KM analysis, WPW and LVNC together was higher risk for the development of significant

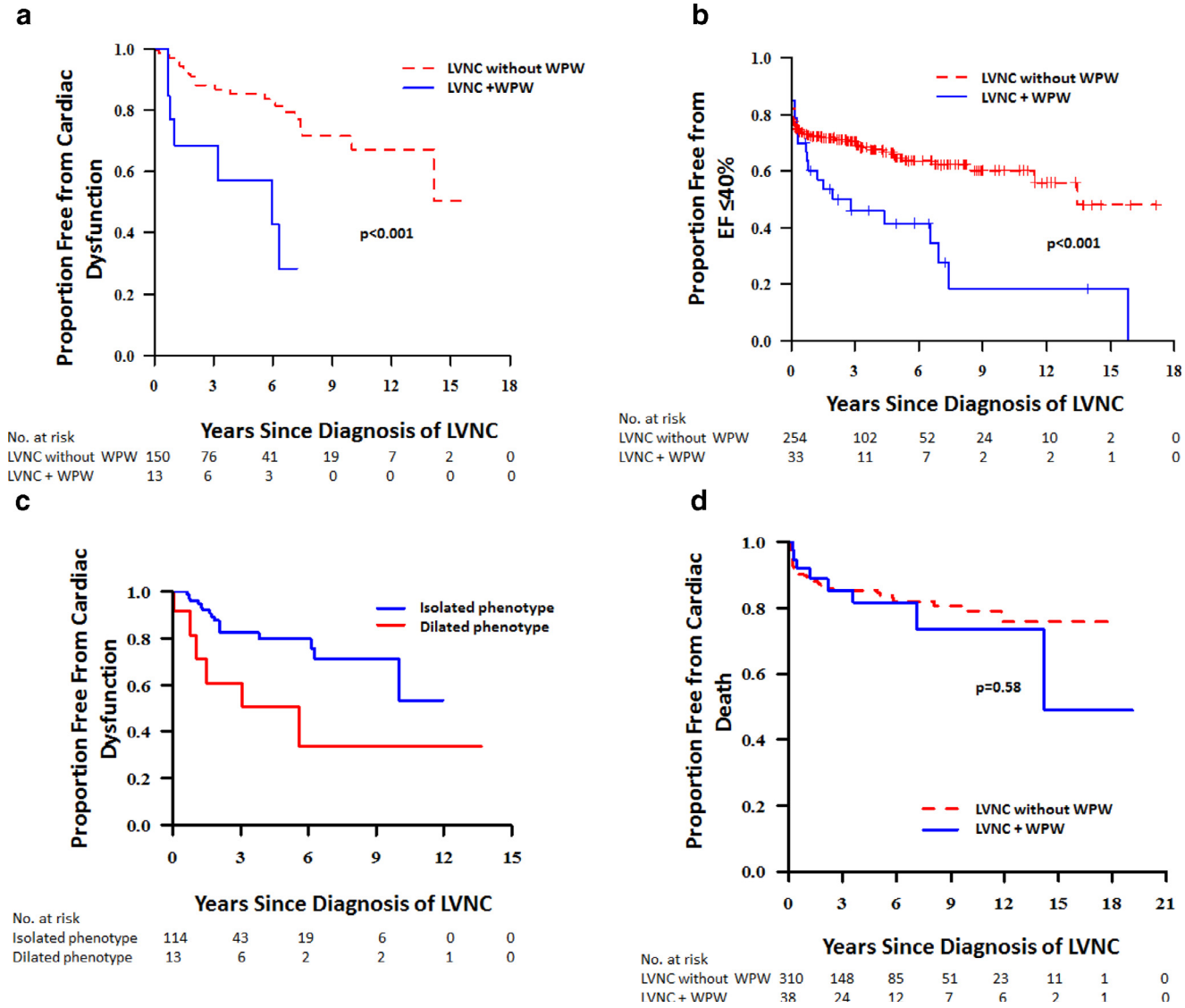

Fig. 1. (**a**) Freedom from cardiac dysfunction in LVNC patients with and without WPW pattern. Kaplan−Meier plot displaying freedom from cardiac dysfunction, defined as EF <55% or SF <−2 *z* scores, in LVNC patients with and without a WPW pattern on electrocardiogram (ECG). Model is limited to those not originally presenting with dysfunction (EF < 55% or SF < −2 *z* scores). (**b**) Freedom from significant cardiac dysfunction (EF ≤ 40%) in LVNC patients with and without WPW pattern. Kaplan−Meier plot displaying freedom from significant cardiac dysfunction, defined as an EF ≤40% in LVNC patients with and without WPW pattern on ECG. Model includes those patients who presented with significant dysfunction (EF ≤ 40%). (**c**) Freedom from cardiac dysfunction in LVNC patients with isolated phenotype versus dilated phenotype. Kaplan−Meier plot displaying freedom from cardiac dysfunction (EF < 55% or SF < −2 *z* scores) in LVNC patients with isolated phenotype versus those with dilated phenotype. Model is limited to those not originally presenting with dysfunction (EF <55% or SF <−2 *z* scores). The *P* value is not displayed secondary to interaction from WPW within the dilated phenotype group. (**d**) Freedom from cardiac death (mortality or heart transplantation) in LVNC patients with and without WPW pattern. Kaplan−Meier plot displaying freedom from cardiac death (mortality or need for heart transplantation) in LVNC patients with and without WPW pattern on ECG. Kaplan−Meier estimation for 3-year freedom from cardiac death is 85.3% (95% CI 90.2, 89.2) for patients with LVNC without WPW and 85.2% (95% CI 67.8, 93.6) for patients with WPW and LVNC.

dysfunction compared with LVNC alone ($P < .001$; Fig. 1b). A Cox analysis was completed to assess risk factors for the development of significant dysfunction and showed WPW to be an independent risk factor (hazard ratio [HR] 4.64 [2.79, 9.90]; $P < .001$; Table 2). A KM analysis was also completed analyzing the risk of developing cardiac dysfunction in patients with a dilated phenotype versus an isolated phenotype. This analysis was stratified by phenotype only and included patients with and without WPW pattern. In univariate analysis, presence of the dilated phenotype was associated with an increased risk of cardiac dysfunction (EF < 55% or SF < −2 *z* scores). However, after accounting for presence of WPW, this did not reach statistical significance (Fig. 1c).

Table 2. Multivariable Cox Regression Model for Outcome of EF ≤ 40*

Parameter	HR (95% CI)†	*P* value	Omnibus *P* value
Age at diagnosis, years			.156
<1	Reference		
1−11	1.30 (0.57, 2.98)		
≥12	0.80 (0.28, 2.27)		
WPW	4.64 (2.79, 9.90)	<.001	
Phenotype			.049
Isolated	Reference	Reference	
Dilated	2.83 (1.18, 6.80)	.020	
Hypertrophied	1.01 (0.37, 2.73)	.988	
Mixed	2.92 (1.02, 8.37)	.046	

*N=212 patients, 30 patients with EF ≤ 40.
†HR (risk of outcome occurring when hazards are proportional).

Mortality

Over the study period, cardiac death, defined as death or cardiac transplantation, occurred in 8 (21%) of the 38 patients with WPW and LVNC. In patients with LVNC without WPW, cardiac death occurred in 43 (13.9%) of patients. Survival analysis for cardiac death showed no statistical difference between the groups ($P = .58$). KM estimation for 3-year freedom from cardiac death is 85.2% (95% CI 67.8, 93.6) for patients with WPW and LVNC, and 85.3% (95% CI 90.2, 89.2) for patients with LVNC without WPW (Fig. 1d).

Ablation Experience

Sixteen patients with WPW and LVNC underwent EP study with 12 undergoing ablation and 10 (83%) achieving successful elimination of pre-excitation. Four patients who were successfully ablated had preceding cardiac dysfunction, all of whom had noted resolution of dyssynchrony with elimination of pre-excitation. Of these, 3 of 4 had improvement of LV function and 1 remained stable. The mean increase in EF was from 44% to 51%. One patient did not have reported EFs post-ablation but was noted to improve from "moderately depressed" to "normal function".

Discussion

Children with LVNC are at an increased risk of major cardiac events including, cardiac dysfunction, arrhythmias, and sudden death.[3,4] WPW alone, increases the risk of SVT, atrial fibrillation, and sudden death.[10,11] WPW has also, in isolation, been reported to be associated with electrical dyssynchrony and the development of cardiac dysfunction.[12,13] Although the association between LVNC and WPW has been reported in previous publications,[4−8] to our knowledge, there has not been a dedicated study to detail the coupling of LVNC and WPW and its clinical repercussions.

Within our large cohort, we found the prevalence of WPW in patients with LVNC to be 11%. This far exceeds the estimated 0.1% to 0.3% prevalence seen in the general population.[10] Patients with LVNC and WPW were more likely to have a dilated phenotype and dysfunction compared with those with LVNC alone. Although we cannot say that WPW is definitively causative of this increased risk, our subgroup analysis of those presenting without dysfunction does suggest that WPW may increase the risk of the development dysfunction over time. This is supported by previous publications showing that WPW, via early activation of ventricular myocardium by the accessory pathway, is associated with dyssynchronous left ventricular contraction and subsequent progressive cardiac dysfunction.[12−14] Furthermore, reports that ablation therapy can result in improved ventricular function lends further support to this assertion,[12,13,15] and in our limited subgroup, ablation was associated with recovery of function. It is possible that in patients with intrinsic myocardial disease, such as in LVNC, dyssynchronous contraction may be even more deleterious than in the general population.

Although both WPW and LVNC are independently known to increase mortality, when comparing those with concomitant LVNC and WPW to those with LVNC without WPW, there was not a significant difference in cardiac death. Further follow-up in this arena will be important.

Study Limitations

This study was a single-center retrospective review and is subject to limitations therein. Although careful attention was given to ensure that all included patients had an appropriate clinical diagnosis of LVNC, inclusion was based on retrospective evaluation of documented criteria. In addition, given our variable length of follow-up, our analysis of dysfunction and survival may harbor time-related limitations. Lastly, given the small number of WPW patients there were potential limitations in statistical power for more granular analysis.

Conclusion

WPW is seen much more frequently in patients with LVNC compared with the general population.[10] Our data suggest that the association of WPW and LVNC portends an increased risk for a dilated phenotype and cardiac dysfunction. Ablation therapy can be performed safely, and in some patients, may result in improvement of cardiac function.

Disclosures

The authors have no disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.09.014.

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