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Short communication

Prevalence and clinical phenotype of concomitant long QT syndrome and arrhythmogenic bileaflet mitral valve prolapse☆

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ABSTRACT

Background: Mitral valve prolapse (MVP), including the recently described arrhythmogenic bileaflet MVP syndrome (ABiMVPS), is associated with repolarization abnormalities and may represent an underestimated cause of sudden cardiac death. The impact of concomitant MVP or ABiMVPS on long QT syndrome (LQTS) clinical severity is unknown.

Methods and results: Retrospective review of 754 LQTS patients [445 females (58%) and mean QTc 471 ± 41 ms] with available echocardiographic data was performed to identify LQTS patients with not only MVP, but also a pro-arrhythmic ABiMVPS phenotype defined as bileaflet MVP, inferolateral T-wave inversions, and frequent complex ventricular ectopy/arrhythmia. As expected, 18/754 (2%) LQTS patients had concomitant MVP. Of these, 5/18 (28%) LQTS patients with MVP satisfied ABiMVPS diagnostic criteria. No difference in symptomatology, degree of QT prolongation, or clinical management was observed between LQTS patients with and without MVP. In contrast, LQTS plus ABiMVPS resulted in a severe cardiac phenotype as illustrated by symptomatic status (LQTS-ABiMVPS; 5/5; 100%; vs LQTS: 279/736; 39%; $p = .008$), degree of baseline QTc prolongation (LQTS-ABiMVPS: 536 ± 58 ms; vs LQTS: 470 ± 40 ms; $p = .009$), and number of patients experiencing ≥1 on-therapy break-through cardiac event (LQTS-ABiMVPS: 4/5; 80%; vs LQTS: 48/736; 7%; $p < .001$]. Lastly, individuals with LQTS plus ABiMVPS were more likely to experience appropriate ICD therapies post-cardiac denervation (LQTS-ABiMVPS: 2/3; 67% vs LQTS: 4/49; 8%; $p = .03$].

Conclusions and relevance: The co-existence of LQTS and ABiMVPS may lead to a rare, but malignant, clinical entity characterized by potentially life-threatening arrhythmias despite maximal LQTS therapy.

1. Introduction

Long QT syndrome (LQTS) is a genetically heterogeneous disorder of cardiac repolarization characterized clinically by QT interval prolongation on 12-lead electrocardiogram (ECG) and an increased propensity for sudden cardiac death (SCD) [1,2]. In exceedingly rare circumstances, the co-existence of genotype-positive LQTS with other SCD-predisposing conditions/substrates such as congenital heart disease [3] and coronary vasospasm [4] have been described in the literature. Although anecdotal, co-existence of LQTS with an additional pro-arrhythmic substrate appears to be associated with a more severe clinical phenotype.

Mitral valve prolapse (MVP) represents one of the most commonly encountered valvular anomalies, affecting an estimated 2%–3% of the general population [5]. In general, MVP is regarded as a benign condition. However, the annual rate of SCD in MVP (0.2%–0.4%/year) [6] is roughly double that observed in the general population (0.1%–0.2%/year) [7]. Although much of this risk is attributable to left ventricular dysfunction in the setting of severe mitral valve regurgitation (MVR) [8], life-threatening ventricular arrhythmias still occur in patients with trivial-to-mild MVR [9]. This phenomena may be explained, in part, by arrhythmogenic bileaflet MVP syndrome (ABiMVPS), a recently described clinical entity with a female predominance characterized clinically by bileaflet MVP, inferolateral T-wave inversions on ECG, high

Abbreviations: ABiMVPS, arrhythmogenic bileaflet mitral valve prolapse syndrome; BCE, break-through cardiac event; ECG, electrocardiogram; LQTS, long QT syndrome; MVP, mitral valve prolapse; MVR, mitral valve regurgitation; QTc, heart rate-corrected QT interval; SCD, sudden cardiac death.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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burden of complex ventricular ectopy/arrhythmia, likely secondary to prolapsing leaflet-induced papillary muscle(s)/inferobasal left ventricle fibrosis, and risk of SCD [10,11].

MVP has been associated with ventricular repolarization abnormalities [12,13] and the expectant background rate of MVP in patients with LQTS has been described previously [14]. Prior to its formal recognition, many patients with ABiMVPS were diagnosed erroneously as "atypical LQTS". As the clinical impact of concomitant MVP has never been assessed in LQTS and given that patients with discernible cardiac channelopathies such as LQTS were excluded from the sentinel ABiMVPS study [10], we sought to ascertain if the phenotypic severity of genotype-positive LQTS is exacerbated by the presence of an additional pro-arrhythmic substrate conferred by either MVP or ABiMVPS.

2. Methods

In this Institutional Review Board-approved study, we conducted a retrospective review of 754 LQTS patients [445 females (58%) and mean heart rate-corrected QT interval (QTc) 471 ± 41 ms] with available echocardiographic data referred for evaluation between January 1999 and July 2016. This cohort was used to identify all LQTS patients with not only MVP, defined as the systolic displacement of one or both leaflets ≥2 mm above the plane of the mitral annulus in a long axis view, observed on transthoracic echocardiogram, but also a pro-arrhythmic ABiMVPS phenotype defined as bileaflet MVP, inferolateral T-wave inversions, and complex ventricular ectopy/arrhythmia. Individuals with a history of complex congenital, ischemic, or rheumatic heart disease as well as a history of mitral valve repair/replacement were excluded.

The following parameters were obtained from the electronic medical records: age, sex, family history of sudden death, syncopal/seizure episodes, LQTS genetic testing results, ECG parameters (i.e. QTc, T-wave inversions, etc.), documented ventricular tachycardia/fibrillation, burden of ventricular ectopy, degree of mitral valve regurgitation, β-blocker status, implantable cardioverter-defibrillator (ICD) status, appropriate/inappropriate ICD shocks, ICD storms, and pertinent surgical interventions such as left/right cardiac sympathetic denervation, and catheter ablation. Putative LQTS-causative rare variants identified in LQTS-ABiMVPS cases were adjudicated according to the 2015 American College of Medical Genetic and Genomics (ACMG) variant classification and reporting standards [15] to provide a contemporary assessment of variant pathogenicity.

JMP ® Pro 10.0.0 (SAS Incorporated, Cary, NC, USA) was employed for statistical analysis. Univariate analysis was used to compare LQTS, LQTS-MVP, and LQTS-ABiMVPS groups on the basis of clinical characteristics. In addition, the clinical characteristics of LQTS-ABiMVPS cases were compared to a small cohort of ABiMVPS cases derived from two recent studies of SCA survivors evaluated at our institution [10,16]. All continuous variables are presented as mean ± SD. The Fisher exact test was used to compare categorical variables, and the Wilcoxon rank-sum/Mann-Whitney *U* test was used to compare continuous variables. For both tests, a $p \leq .05$ was considered statistically significant. All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the article as written.

3. Results

Similar to population frequency, 18/754 (2%) qualifying LQTS patients had concomitant MVP. Of these, 5/18 (28%) LQTS-MVP patients satisfied the diagnostic criteria for ABiMVPS. Clinical characteristics of patients with isolated LQTS ($n = 736$), LQTS-MVP ($n = 13$), and LQTS-ABiMVPS ($n = 5$) are summarized in Table 1.

Analysis of symptomatology, electrocardiographic parameters, therapy requirements, and break-through cardiac events (BCEs such as cardiogenic syncope/seizures, aborted cardiac arrest, appropriate ventricular fibrillation-terminating ICD shocks, and SCD) indicate that LQTS-MVP is virtually indistinguishable clinically from isolated LQTS (Table 1). However, LQTS-MVP individuals were more likely to have isolated PVCs on ambulatory Holter monitoring than those with isolated LQTS (LQTS-MVP: 7/13; 54% vs LQTS: 25/212; 12%; $p < .001$).

In contrast, LQTS-ABiMVPS results in a more severe/pro-arrhythmic clinical phenotype as illustrated by symptomatic status (LQTS-ABiMVPS; 5/5; 100%; vs LQTS: 279/736; 39%; $p = .008$), likelihood of sentinel cardiac arrest (LQTS-ABiMVPS: 3/5; 60%; vs LQTS: 26/736; 4%; $p \leq .001$), degree of baseline QTc prolongation (LQTS-ABiMVPS: 536 ± 58 ms; vs LQTS: 470 ± 40 ms; $p = .009$), number experiencing ≥1 BCEs (LQTS-ABiMVPS: 4/5; 80%; vs LQTS: 48/736; 7%; $p < .001$), and presence of non-sustained ventricular tachycardia with a right bundle branch block (RBBB) morphology on ambulatory Holter monitoring (LQTS-ABiMVPS: 3/5; 60% vs LQTS: 0/212; 0%, $p < .001$; Table 1).

As a result of recurrent ventricular arrhythmias, LQTS-ABiMVPS patients were more likely to receive both left and bilateral cardiac sympathetic denervation (Table 1). Unlike isolated LQTS, LQTS-ABiMVPS patients that required cardiac sympathetic denervation(s) often continued to experience appropriate implantable cardioverter-defibrillator (ICD) therapies post-procedure (LQTS-ABiMVPS: 2/3; 67%; vs LQTS: 4/49 8%; $p = .03$]. Case descriptions, including LQTS genotypes, for LQTS-ABiMVPS patients are detailed in Table 2 and Supplemental Fig. 1.

Interestingly, no family history of either single leaflet or bileaflet MVP prolapse was observed in LQTS-ABiMVPS cases. A family history of LQTS was observed in two LQTS-ABiMVPS individuals and two LQTS-ABiMVPS cases had sporadic/de novo LQTS-causative variants. LQTS-ABiMVPS pedigree structures and ACMG variant classifications are detailed in Supplemental Fig. 2.

Lastly, to ascertain the degree of phenotypic similarity between LQTS-ABiMVPS and those with isolated ABiMVPS, the clinical characteristics of LQTS-ABiMVPS patients were compared to a small cohort of SCA survivors diagnosed with ABiMVPS derived from two recent studies [10,16]. Interestingly, aside from the degree of QT prolongation (LQTS-ABiMVPS: 536 ± 58 ms; vs ABiMVPS: 438 ± 19 ms; $p = .001$) and number of patients undergoing bilateral sympathetic denervation (LQTS-ABiMVPS: 2/5; 40%; vs ABiMVPS: 0/21; 0%; $p = .004$), no significant differences were observed (Supplemental Table 1).

4. Discussion

Although ventricular repolarization abnormalities, including mild QT prolongation and dispersion, have been associated with MVP [12,13], this study suggests that the co-existence of MVP, in the absence of a distinct ABiMVPS phenotype, does not impact LQTS clinical severity. However, the pro-arrhythmic substrate(s) generated by concomitant genotype-positive LQTS and ABiMVPS appears to result in a severe and often recalcitrant cardiac phenotype characterized by the persistence of potentially life-threatening ventricular arrhythmia despite maximal LQTS therapy.

Notably, LQTS-ABiMVPS accounted for a third of LQTS patients included in this study that would be considered denervation non-responders as they continued to experience BCEs post-denervation. Not surprisingly, severe forms of congenital LQTS, including calmodulinopathic LQTS, Jervell and Lange-Nielson syndrome, and Timothy syndrome, accounted for the majority of the remaining two thirds. Thus, the severity of the pro-arrhythmic substrate(s) present in LQTS-ABiMVPS appears to be akin to that associated with the most severe and penetrant forms of congenital LQTS.

Unfortunately, some LQTS-ABiMVPS cases (i.e. #2 and #4) have experienced recurrent ventricular arrhythmias, potentially attributable to both pro-arrhythmic substrates, despite beta-blockade, mexiletine/home continuous lidocaine infusion, bilateral denervation, intentional atrial pacing (lower rate limits at 80), and targeted PVC ablation. As recurrent ventricular fibrillation is commonly observed in ABiMVPS [10], it is not entirely surprising that the severity of the clinical/arrhythmic phenotype observed in LQTS-ABiMVPS is more in line with that observed in SCA survivors with ABiMVPS [10,16] than isolated LQTS. However, despite the small sample size, the degree of QT prolongation and number of appropriate break-through ICD therapies, some secondary to sustained *torsades de pointes*, observed in LQTS-ABiMVPS patients makes it difficult to conclude definitively that the severe cardiac phenotype observed in these cases is entirely secondary to ABiMVPS and not the result of a synergistic disease process.

Regardless, this study demonstrates that two rare pro-arrhythmic substrates, LQTS and ABiMVPS, can co-exist and emphasizes the need

Table 1
Clinical characteristics of LQTS, LQTS-MVP, and LQTS-ABiMVPS cases.

Demographic	LQTS (n = 736)	LQTS-MVP (n = 13)	p value[a]	LQTS-ABiMVPS (n = 5)	p value[a]
General/symptoms					
Female, n (%)	430/736 (58)	11/13 (73)	.09	4/5 (80)	.4
Symptomatic[b], n (%)	279/736 (39)	4/13 (31)	.8	5/5 (100)	.008
Sentinel SCA, n (%)	26/736 (4)	0/13 (0)	1	3/5 (60)	<.001
ECG					
QTc, ms	470 ± 40	482 ± 42	.2	536 ± 58	.009
Ambulatory Holter monitoring[c]					
Isolated PVCs, n (%)	25/212 (12)	7/13 (54)	<.001	5/5 (100)	<.001
PVCs in bigeminy, n (%)	4/212 (2)	1/13 (8)	.3	4/5 (80)	<.001
NSVT, n (%)	0/212 (0)	1/13 (8)	.06	3/5 (60)	<.001
SVT/VF, n (%)	0/212 (0)	0/13 (0)	1	0/5 (0)	1
NSVT morphology					
LBBB inferior axis, n (%)	0/212 (0)	0/13 (0)	1	0/3 (0)	1
LBBB superior axis, n (%)	0/212 (0)	1/13 (8)	.06	0/3 (0)	1
RBBB inferior axis, n (%)	0/212 (0)	0/13 (0)	1	2/3 (66)	<.001
RBBB superior axis, n (%)	0/212 (0)	0/13 (0)	1	3/3 (100)	<.001
Echocardiography					
Mitral valve prolapse, n (%)	0/736 (0)	13/13 (100)	<.001	5/5 (100)	<.001
Anterior leaflet only, n (%)	–	2/13 (15)	–	0/5 (0)	–
Posterior leaflet only, n (%)	–	6/13 (46)	–	0/5 (0)	–
Bileaflet, n (%)	–	5/13 (39)	–	5/5 (100)	–
Therapy					
β-Blocker, n (%)	686/736 (93)	11/13 (85)	.2	5/5 (100)	1
ICD placement, n (%)	178/736 (24)	4/13 (8)	.2	4/5 (80)	.01
Left cardiac sympathetic denervation, n (%)	124/736 (17)	1/13 (8)	.5	3/5 (60)	.04
Subsequent right cardiac sympathetic denervation, n (%)	7/736 (1)	0/13 (0)	1	2/5 (40)	.001
VT/VF ablation, n (%)	8/736 (1)	0/13 (0)	1	1/5 (20)	.06
Therapy breakthrough					
≥1 break-through cardiac event(s)[d], n (%)	48/736 (7)	0/13 (0)	.6	4/5 (80)	<.001
Appropriate break-through ICD therapies, n (%)	11/178 (6)	0/4 (0)	1	4/4 (100)	<.001
Break-through ICD storm(s), n (%)	4/178 (2)	0/4 (0)	1	1/4 (25)	.1
Appropriate post-denervation ICD therapies, n (%)	4/49 (8)	0/1 (0)	1	2/3 (67)	.03

Abbreviations: ABiMVPS, arrhythmogenic bileaflet mitral valve prolapse syndrome; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LQTS, long QT syndrome; MVP, mitral valve prolapse; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular contractions; QTc, heart rate-corrected QT interval; RBBB, right bundle branch block; SCA, sudden cardiac arrest; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia; and VF, ventricular fibrillation.
[a] Statistical analysis compared LQTS plus MVP and LQTS plus ABiMVPS individually with isolated LQTS.
[b] Symptoms were defined as syncope, seizures, and/or sudden cardiac arrest.
[c] Ambulatory Holter monitoring data was only available for 212/736 LQTS patients with echocardiograms.
[d] Break-through cardiac events defined as cardiogenic syncope/seizure, aborted cardiac arrest, appropriate ICD therapies/ICD storm, SCA, and SCD.

to consider concomitant disorders in LQTS patients expressing unexpectedly severe and recalcitrant phenotypes. As catheter ablation [17] and early mitral valve repair/replacement [18] may reduce the ectopy/arrhythmia burden associated with ABiMVPS, further study is needed to determine if these modalities can reduce the number of BCEs in LQTS-ABiMVPS patients with recurrent ventricular arrhythmia despite maximal LQTS therapy.

5. Conclusion

This study provides the first evidence that co-existence of LQTS and ABiMVPS may result in a rare, but malignant, clinical entity, characterized by potentially life-threatening arrhythmias that breakthrough maximal LQTS-directed treatment programs comprising combination drug-, denervation-, and device-therapy. Further study is needed to

Table 2
Case descriptions of patients with genotype-positive LQTS and concomitant ABiMVPS.

Clinical characteristics/genetics					ECG		Holter		TTE		Therapy and breakthrough(s)				
ID	Sex	Sentinel event	LQTS variant	ACMG classification[a]	QTc (ms)	TWI	Mean VE/hr	NSVT	MVR	LVEF (%)	BB	ICD	CSD	ICD shock(s)	Post-CSD BCE (s)
1	M	SCA (age 49)	T322A-KCNQ1 (LQT1)	Pathogenic (ii)	507	Yes	1	No	Mild	68	Yes	Yes	Yes	Yes	No
2	F	Near drowning (age 12)	R366W-KCNQ1 (LQT1)	Pathogenic (ii)	609	Yes	72	Yes	Trivial	59	Yes	Yes	Yes	Yes	Yes
3	F	SCA (age 24)	T421M-KCNH2 (LQT2)	Pathogenic (ii)	569	Yes	78	Yes	Mod.	60	Yes	No[b]	No	N/A	N/A
4	F	SCA (age 1)	F1486L-SCN5A (LQT3)	Pathogenic (iiib)	540	Yes	1052	Yes	None	56	Yes	Yes	Yes	Yes	Yes
5	F	Syncope (age 23)	D76N-KCNE1 (LQT5)	Pathogenic (ii)	457	Yes	102	No	Trivial	62	Yes	No	No	Yes	N/A

Abbreviations: ACMG, American College of Medical Genetics and Genomics; ABiMVPS, arrhythmogenic bileaflet mitral valve prolapse syndrome; BB, beta-blocker; BCE, break-through cardiac event; CSD, cardiac sympathetic denervation; ECG, electrocardiogram; ICD, implantable defibrillator-cardioverter; ID, identification; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; MVR, mitral valve regurgitation; NSVT, non-sustained ventricular tachycardia; QTc, heart-rate corrected QT interval; SCA, sudden cardiac arrest; TTE, transthoracic echocardiography; TWI, T-wave inversions; and VE, ventricular event.
[a] The specific ACMG criteria used in the adjudication of these variants is detailed in Supplemental Fig. 1.
[b] Patient was offered an ICD for secondary prevention of sudden cardiac death, but opted for continued beta-blocker therapy and a home automatic external defibrillator as she had not experienced any cardiac symptomatology since entering menopause.

determine the molecular mechanisms that differentiate ABiMVPS from benign MVP and whether interventions for ABiMVPS (i.e. ablation, mitral valve replacement, etc.) can reduce the burden of breakthrough cardiac events that occurs in patients with LQTS-ABiMVPS despite all conventional LQTS therapies.

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Dr. Ackerman is a consultant for Audentes Therapeutics, Boston Scientific, Gilead Sciences, Invitae, Medtronic, MyoKardia, and St. Jude Medical. From 2004 to 2016, M.J.A. and Mayo Clinic received sales-based royalties from Transgenomic for their FAMILION-LQTS and FAMILION-CPVT genetic tests. M.J.A. and Mayo Clinic have an equity/royalty relationship (without remuneration so far) with AliveCor, Blue Ox Health, and StemoniX. However, none of these entities participated in this study. The other authors have no conflicts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.046.

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