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Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum★

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Abstract

Background: Sudden cardiac arrest (SCA) may be the sentinel expression of a sudden cardiac death-predisposing genetic heart disease (GHD). Although shown to underlie many unexplained SCAs in the young, the contribution of GHDs to sentinel SCA has never been quantified across the age spectrum. Thus, we sought to determine the contribution of GHDs in single-center referral cohort of non-ischemic SCA survivors.

Methods and results: Retrospective analysis of 3037 patients was used to identify all individuals who experienced a sentinel event of SCA. Following exclusion of patients with ischemic or complex congenital heart disease, cases were classified by clinical diagnoses. Overall, 180 (5.9%) referral patients experienced a sentinel SCA (average age at SCA 28 ± 15 years, 99 females). An etiology was identified in 113/180 patients (62.8%) including channelopathies in 26.7%, arrhythmogenic bileaflet mitral valve prolapse in 10.6%, cardiomyopathies in 9.4%, other etiologies in 6.7%, acquired long QT syndrome in 6.7%, and multiple disorders in 2.8%. The remaining 67/180 (37.2%) cases were classified as idiopathic ventricular fibrillation (IVF).

★Both 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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Conflict of interest disclosures

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. Dr. Giudicessi declares no conflicts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.05.100>.

Interestingly, the contribution of GHDs declined precipitously after the first decade of life [90.0% (age 0–9; n = 20), 58.7% (age 10–19; n = 46), 28.1% (age 20–29; n = 32), 23.8% (age 30–39; n = 42), 16.7% (age 40–49; n = 24), and 12.5% (age 50+; n = 16)].

Conclusions: Within a referral population enriched for GHDs, the ability of a comprehensive cardiac evaluation, including genetic testing, to elucidate a root cause in non-ischemic SCA survivors declined with age. Although rare, GHDs can underlie SCA into adulthood and merit consideration across the age spectrum.

Keywords

Arrhythmia; Cardiomyopathy; Genetics; Genetic testing; Sudden cardiac arrest; Sudden cardiac death

1. Introduction

Sudden cardiac death (SCD), defined as death due to a cardiovascular etiology 1 h after symptom onset, affects all age groups and accounts for ~350,000 deaths in the United States annually [1]. Although the vast majority of SCD occurs in older individuals and is attributable to arrhythmic sequelae of coronary artery disease [2,3], the incidence of SCD in infants, children, and young adults <40 years of age has been estimated at 1–8/100,000 individuals annually. Although much smaller in sheer numbers, the loss of life-years associated with sudden unexplained death in the young (SUDY) rivals that of most individual cancers and ischemic heart disease [4].

In SUDY victims and to larger extent, young (<40 years of age) nonischemic sudden cardiac arrest (SCA) survivors, genetic heart diseases (GHDs), specifically hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), have a predominant role [5–7]. However, the precise contribution of specific GHDs, as well as more recently described clinical entities such as arrhythmogenic bileaflet mitral valve prolapse syndrome (ABiMVPS) [8] and triadin knock-out syndrome (TKOS) [9], to sentinel non-ischemic SCA across the entire age-spectrum remains poorly defined.

As such, this study sought to determine and compare the contribution of GHDs to sentinel SCA across the age spectrum as well as the yield of genetic testing in a unique GHD-enriched single center referral cohort composed of both pediatric and adult non-ischemic SCA survivors.

2. Methods

2.1. Study population and definitions

In this Institutional Review Board-approved single-center study, the electronic medical records of 3037 consecutive patients referred to Mayo Clinic's Genetic Heart Rhythm Clinic between January 1999 and April 2017 were reviewed retrospectively to identify all individuals who experienced a sentinel event of SCA. For the purposes of this study, SCA was defined as a witnessed or unwitnessed collapse that required external de-fibrillation

from a shockable rhythm (either ventricular fibrillation or pulseless ventricular tachycardia) as part of the successful resuscitation efforts. A SCA was considered sentinel if there was no prior diagnosis or clinical suspicion for an underlying SCD-predisposing heart disease. In order to examine the relative contribution of GHDs to sentinel SCA across the age-spectrum, SCA survivors were stratified by age at the time of SCA to allow for comparison between pediatric (SCA < 18 years of age) and adult (SCA ≥ 18 years of age) SCA survivors and by decade of life (age 0–9 years, age 10–19, age 20–29, age 30–39, age 40–49, and age 50+). Following exclusion of patients who suffered non-cardiac arrests and those with ischemic or complex congenital heart disease, 180 SCA survivors were included in the final analysis.

2.2. Clinical evaluation and diagnosis

Regardless of whether the patient presented initially to Mayo Clinic or a referring institution, a detailed clinical history, including family history, prescription/illegal drug use, prior symptomatology, and SCA circumstance(s) was obtained independently for all cases. A comprehensive cardiovascular evaluation, including physical examination, complete metabolic panel, resting 12 lead electrocardiogram, and transthoracic echocardiography, was performed as recommended previously [10]. Exercise testing was performed when the sentinel SCA was felt to be adrenergically-mediated or CPVT or LQTS was suspected. Appropriate advanced cardiac imaging (cardiac magnetic resonance imaging, computed tomography, positron emission tomography, etc.) was obtained if an arrhythmogenic, inflammatory, or infiltrative cardiomyopathy was suspected. Coronary angiography was pursued, typically by referring providers at the time of presentation, if coronary artery disease, coronary artery anomalies, coronary vasospasm, or spontaneous coronary artery dissection was considered a possibility. Additional testing, including but not limited to pharmacologic challenge for either LQTS or the J-wave syndromes (JWS) including Brugada syndrome (BrS), diagnostic electrophysiology studies, and right ventricular biopsy, were obtained on a case-by-case basis.

All diagnoses were rendered, when possible, on the basis of established expert-consensus clinical diagnostic criteria (i.e. LQTS Schwartz score [11], ARVC task-force criteria [12], etc.) and recent statements/guidelines [13]. In the absence of formal diagnostic criteria/guidelines, recently described clinical entities were diagnosed using sentinel phenotypic profiles (i.e. bileaflet mitral valve prolapse on echocardiogram, inferior T-wave inversions on 12 lead ECG, and frequent complex ventricular ectopy of outflow tract/papillary muscle origin of ambulatory Holter monitor for ABiMVPS and extensive T-wave inversions in leads V₁–V₄ on 12 lead ECG, cardiac arrest in early childhood, and recessive inheritance of homozygous/compound heterozygous truncating genetic variation in *TRDN*-encoded triadin for TKOS). When the diagnostic criteria for a specific disease were met, a “certain” diagnosis was rendered. For those cases that partially met diagnostic criteria for a specific disease or where formal diagnostic criteria do not exist currently, a “probable” diagnosis was assigned if sufficient evidence was available to exclude all other potential causes. SCA survivors, with documented ventricular fibrillation (VF) and no evidence of an underlying respiratory, metabolic, or toxicological etiologies, in whom a certain, probable, or suspected cardiovascular diagnosis could not be rendered following a comprehensive clinical evaluation, including genetic testing, received a diagnosis of idiopathic VF (IVF) in

accordance with the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asian Pacific Heart Rhythm Society joint expert consensus guidelines [13].

2.3. Genetic assessment

When the clinical picture was consistent with or suspicious for an underlying GHD, commercial- or in very rare cases laboratory-based genetic testing was pursued. At a minimum, the following major/strong evidence genes were examined: *DSC2*, *DSG2*, *DSP*, and *PKP2* for arrhythmogenic right ventricular cardiomyopathy (ARVC); *RYR2* and *CASQ2* for *CPVT*; *LMNA*, *SCN5A*, and *TNNC1* for dilated cardiomyopathy (DCM); *MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, and *TPM1* for hypertrophic cardiomyopathy (HCM); *SCN5A* for *JWS*; and *KCNQ1*, *KCNH2*, and *SCN5A* for *LQTS*. In some cases, commercial extended disease-specific, pan-arrhythmia/cardiomyopathy, or pan-cardiac gene panels were utilized.

Ultra-rare variants (minor allele frequency (MAF) < 0.005) identified in unexplained SCA/IVF cases were classified using the 2015 American College of Medical Genetics and Genomics guidelines [14] to allow for a contemporary assessment of the prevalence and spectrum of “likely pathogenic” and “pathogenic” variants.

2.4. Statistical approach

JMP® Pro 10.0.0 (SAS Incorporated, Cary, NC, USA) was employed for statistical analysis. All continuous variables are presented as mean $\pm$ 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 two-tailed value of $p < 0.05$ was considered statistically significant. Both authors had full access to and take full responsibility for the integrity of the data.

3. Results

3.1. Baseline demographics and clinical diagnoses in non-ischemic sudden cardiac arrest survivors

Overall, 180/3037 patients (5.9%; 99 females; average age at SCA 28.0 ± 15.4 years) without evidence of ischemic or complex congenital heart disease were referred to Mayo Clinic’s Genetic Heart Rhythm Clinic for evaluation after experiencing a sentinel SCA (Table 1). Following comprehensive cardiovascular evaluation, a certain or probable clinical diagnosis was rendered in 113/180 SCA survivors (62.8%; Table 1). This included a cardiac channelopathy in 26.7%, ABiMVPS in 10.6%, cardiomyopathy in 9.4%, acquired/drug-induced LQTS (aLQTS) in 6.7%, and multiple disorders in 2.8% as summarized in Fig. 1. Collectively, 71/113 (62.8%) SCA survivors (40 pediatric and 31 adult) that received a certain or probable diagnosis had an underlying SCD-predisposing GHD (Table 1). Specific cardiac channelopathies, cardiomyopathies, and other clinical etiologies diagnosed in pediatric and adult SCA survivors are detailed in Supplemental Table 1. In the remaining 67/180 (37.2%) SCA survivors (11 pediatric and 56 adult), the root cause of the SCA could not be identified following comprehensive cardiovascular evaluation. As such, these unexplained SCA cases were classified as IVF (Fig. 1). The specific clinical investigations

undertaken in unexplained SCA survivors who were ultimately labelled as IVF are summarized in Supplemental Table 2.

3.2. Comparison of baseline demographics and diagnostic yield between pediatric and adult sudden cardiac arrest survivors

Collectively, no significant difference in the number of witnessed arrests, arrest location, or initiation of by-stander cardiopulmonary resuscitation was observed between pediatric and adult SCA survivors (Table 1).

In comparison to adult SCA survivors ($n = 127$; average age at SCA 35.3 ± 11.9 years), pediatric SCA survivors ($n = 53$; average age at SCA 10.5 ± 5.8 years) were more likely to experience an emotion- or exertion-triggered SCA [27/53 (50.9%) vs. 29/127 (22.8%), $p = 0.0003$] and receive a SCA-causative GHD diagnosis [40/53 (75.5%) vs. 31/127 (24.4%), $p < 0.0001$] (Table 1). Specifically, pediatric SCA survivors were more likely to be diagnosed with an underlying cardiac channelopathy, most commonly CPVT, LQTS, or TKOS (Supplemental Table 1), in comparison to their adult SCA counterparts [31/53 (58.5%) vs. 17/127 (13.4%), $p < 0.0001$] (Fig. 1). The top five diagnoses rendered in pediatric SCA survivors within this GHD-enriched referral cohort were LQTS (28.3%), CPVT (20.8%), IVF (20.8%), HCM (5.7%), and TKOS (5.7%).

In contrast, adult SCA survivors were more likely to experience their sentinel SCA at rest [89/127 (70.1%) vs. 19/53 (35.9%), $p < 0.0001$] (Table 1) and receive a diagnosis of ABiMVPS [18/127 (14.2%) vs. 1/53 (1.9%), $p = 0.02$], aLQTS [12/127 (9.4%) vs. 0/53 (0.0%), $p = 0.02$], or IVF [56/127 (44.1%) vs. 11/53 (20.8%), $p = 0.005$] in comparison to pediatric SCA survivors (Fig. 1). The top five diagnoses rendered in adult SCA survivors were IVF (44.1%), ABiMVPS (14.2%), aLQTS (9.4%), LQTS (7.9%), and J-wave syndromes (3.9%).

A complete list of certain and probable genetic and non-genetic diagnoses rendered in both the pediatric and adult non-ischemic SCA survivors are summarized in Supplemental Table 1.

3.3. Yield of genetic testing and genetic findings in pediatric and adult sudden cardiac arrest survivors

Genetic testing was pursued in 125/180 (69.4%) of SCA survivors. The vast majority of SCA survivors that received a certain or probable GHD diagnosis underwent some form of genetic testing [69/71 (97.2%)], most frequently diagnostic disease-specific genetic testing. The yield of genetic testing was comparatively high for both pediatric [34/40 (85.0%)] and adult [24/29 (82.8%)] SCA survivors with GHD diagnoses. Not surprisingly, the yield of genetic testing was significantly higher in SCA survivors who received a certain rather than probable GHD diagnosis [46/49 (93.9%) vs 12/20 (60.0%), $p = 0.001$]. Putative GHD-causative genetic variants identified in pediatric and adult SCA survivors are detailed in Supplemental Table 3 and Supplemental Table 4, respectively. The proportion of GHD-mediated SCA cases found subsequently to have either a family history of sudden death, clinically affected relatives, or a disease-causative de novo genetic variant is outlined, by GHD, in Supplemental Table 5.

Commercial genetic testing was also pursued in 49/67 (73.1%) unexplained SCA survivors (i.e. those designated as IVF). However, due to the retrospective nature of this study a standardized panel of genes was not utilized. Nevertheless, the yield of clinically actionable genetic findings [i.e. variants designated as either “pathogenic” or “likely pathogenic” according to ACMG guidelines] was low among these unexplained SCA survivors [1/49 (2.0%); Table 2]. Although several variants of uncertain significance (VUS) identified in unexplained SCA survivors (p.Arg625Cys-CACNB2, p.Gly924Ala-KCNH2, p.Glu30Gly-SCN5A, p.Val146Met-SCN5A, and p.Pro648Leu-SCN5A) were observed previously in SCD-predisposing GHD and/or autopsy-negative sudden unexplained death cases [15–21], only p.Glu243Lys-RYR2 was deemed to be clinically actionable (i.e. met ACMG criteria for classification as either a “likely pathogenic” or “pathogenic” variant) as a result of an over-representation in CPVT cases versus public exomes [22] (Table 2). A list of ultra-rare (minor allele frequency < 0.005) variants identified in individuals with an IVF diagnosis is provided in Table 2.

3.4. Contribution of genetic heart disease to sentinel non-ischemic cardiac arrest across the age spectrum

In order to more closely assess temporal patterns associated with the disorders underlying sentinel non-ischemic SCA, GHDs, non-GHDs, and IVF diagnoses were pooled and the diagnostic yield assessed by decade of life at the time of SCA (Fig. 2). Notably, after the first decade of life (age 0–9 years), the diagnostic yield of SCA/SCD-predisposing GHDs declined precipitously (Fig. 2). However, 1 GHD-mediated sentinel SCA was observed in patients who presented in their 30s, 40s, and 50s.

Conversely, an inverse trend was observed for both IVF and non-GHDs (Fig. 2). As such, in this unique GHD-enriched referral cohort, the ability of a comprehensive cardiovascular evaluation, including genetic testing in many instances, to ascertain the root cause of a sentinel SCA in patients without complex congenital or ischemic heart disease was highly age-dependent and subject to distinct age-related temporal patterns (Fig. 2).

4. Discussion

4.1. GHDs: a frequent contributor to sentinel SCA across the age-spectrum

In this single center GHD-enriched referral cohort of sentinel SCA survivors without complex congenital or ischemic heart disease, 39.4% of all patients and 62.8% of patients who received a certain or probable clinical diagnosis had an underlying GHD. Consistent with prior studies [6], the yield of GHDs in pediatric SCA survivors was high accounting for 90% of SCAs that occurred during the first decade of life. Notably, although the contribution of GHDs declined precipitously with each subsequent decade of life, SCD-predisposing GHDs were identified in 1 sentinel SCA survivor that presented in their 30s, 40s, or 50s.

Unfortunately, the referral nature of this study cohort makes extensive generalizations difficult. However, the observation that sentinel GHD-mediated SCAs can occur well into adulthood, underscores the need to better define the contribution of GHDs at the population-

level. This is particularly important among young adult SCA survivors (ages 18–40) where the rate of coronary events is anticipated to be lower.

To this end, a recent single-center prospective study of predominantly adult French out-of-hospital cardiac arrest (OHCA) survivors demonstrated that GHDs accounted collectively for 2.4% of all OHCA and 3.9% of OHCA with a cardiac cause [23]. However, unlike the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER) [5], pursuit of drug provocation studies was left to the discretion of individual physicians and the utility of genetic testing was not examined [24]. Therefore, a fraction of the unexplained SCA cases (~2.5%) in the aforementioned Assistance Publique Hôpitaux de Paris OHCA registry [23] could be secondary to clinically concealed GHDs, namely cardiac channelopathies and pre-clinical cardiomyopathies.

Although large-scale prospective investigations are needed to define the true contribution of GHDs to sentinel SCA, it is becoming increasingly clear that the collective contribution of GHDs to SCA in adulthood is not insignificant. As such, this study further emphasizes the need for healthcare providers involved in the immediate and follow-up care of SCA survivors to keep SCA-predisposing GHDs in the differential diagnosis and pursue the clinical work-up, including drug provocation and genetic testing, needed to rule out GHDs in patients of all ages who suffer a sentinel SCA in the setting of an otherwise structurally normal heart.

4.2. Gender differences and risk of non-ischemic SCA

The risk of SCA/SCD in females, perhaps due to atheroprotective effects of estrogen, has been shown previously to be roughly half that of age-matched males [25,26]. Even once coronary heart disease (i.e. acute coronary syndromes, ischemic scarring, etc.) is removed, a smaller, but persistent, male predominance has still been observed across younger SCA survivors and SCD victims [5,24,27]. Of note, the absence of discernible diagnostic patterns or other means to explain the persistence of this gender difference has led some to speculate that females may experience a “gender-advantage” that extends to other cardiovascular diseases, including GHDs such as the cardiomyopathies and channelopathies [26].

In contrast to prior studies, the current study displays a slight female predominance (55% female vs. 45% male) overall. However, this phenomenon appears to be well-explained by an overrepresentation of females in three of the most common diagnoses rendered: i) cLQTS (13.9% of all non-ischemic SCA; 72% female), ii) ABiMVPS (10.6% of all non-ischemic SCA; 89% female), and iii) aLQTS (6.7% of all nonischemic SCA; 69% female). Given the known effect of estrogen on cardiac repolarization reserve [28], it comes as little surprise that the majority of cLQTS (83%) and acquired/drug-induced LQTS (100%) were in their reproductive years (i.e. post-pubertal/pre-menopausal) at the time of their sentinel SCA. Furthermore, the female-predominant nature of ABiMVPS is consistent with previous reports [8,29], but the pathophysiology of this observed gender difference remains poorly explained.

Interestingly, when ABiMVPS and all forms of LQTS are removed, a male predominance (57% male vs. 43% female) emerges that is similar to the non-ischemic SCA etiology

studies of Mellor et al. (56%) [24] and Geri et al. (63%) [23]. As such, it appears that an enrichment of ABiMVPS and LQTS is responsible, at least in part, for the observed gender distribution and reinforces the inherent limitations associated with this single-center referral cohort. Nevertheless, this study suggests that a female “gender-advantage” does not extend to all SCD-predisposing disorders as previously hypothesized [26] and that increased granularity is needed to fully understand the role gender plays in non-ischemic SCA/SCD risk.

4.3. Utility of genetic testing in sentinel and unexplained SCA

In this study, the yield of either “likely pathogenic” or “pathogenic” variants following either phenotype-driven genetic testing or broader gene panel genetic testing was highly dependent on whether or not a clinical GHD phenotype was identified. As the yield of genetic testing is correlated strongly with phenotypic strength, it should come as little surprise that the yield of genetic testing was low (2.0%) in those deemed to have suffered an unexplained SCA (i.e. IVF).

A similar genetic testing yield was also observed in the recent unexplained SCA/IVF sequencing studies by Mellor et al. [13/102 (12.8%)] [24], Visser et al. [1/33 (3.0%)] [30], and Leinonen et al. [7/76 (9.2%)] [31]. The decreased yield of genetic testing in our study is likely due, at least in part, to lower utilization of broad multi-phenotype genetic testing (i.e. pan-cardiac or clinical/research-based whole exome sequencing) known to increase both the number of likely pathogenic/pathogenic variants and variants of uncertain significance (VUS) identified [24].

However, discordant variant adjudication may also play a role. As demonstrated recently in HCM, discordant classifications were observed in 23/112 (20.5%) of variants adjudicated by Sarcomeric Human Resource Consortium (SHaRe) consortium member institutions and an astounding 315/695 (45.2%) of variants adjudicated by clinical laboratories contributing to the Clinical Variant (ClinVar) database [32]. Although privately held and outdated data were the major culprits, differences in expert assessment of clinical, genetic, and functional data also contributed [32].

Regardless of the ultimate cause(s) for the variability of genetic testing yield across the unexplained SCA/IVF studies, all such studies have demonstrated that the yield of genetic testing in SCA survivors without a discernible clinical phenotype is low. As the likelihood of encountering 1 VUS, particularly with pan-cardiac or clinical whole exome sequencing, exceeds exponentially the likelihood of unearthing a clinically actionable likely pathogenic/pathogenic variant in a SCA-predisposing GHD-susceptibility gene, the decision to pursue genetic testing in unexplained SCA/IVF cases should not be taken lightly. As such, genetic testing in unexplained SCA/IVF is best accomplished in the setting of dedicated cardiovascular genetics clinics equipped with the infrastructure and expertise needed to carefully interpret, continually reappraise, and if needed act on genetic findings identified in the context of ambiguous clinical phenotypes.

4.4. Unexplained SCA (IVF): truly idiopathic?

Overall, 37.2% of all SCA survivors and 44.1% of adult SCA survivors referred to our institution's Genetic Heart Rhythm Clinic remained unexplained following comprehensive cardiovascular evaluation. At first glance, these numbers appear to be relatively high. However, national registries such as CASPER (44%) [5] and other tertiary medical center referral cohorts (39%) [6] have reported similar numbers that are substantially higher than those observed in population-based SCA/SCD studies (~3%–7%) [23,33]. As such, registry and referral cohorts of unexplained SCA survivors represent an enriched resource in the quest to better understand the mechanisms and clinical etiologies underlying so-called IVF.

Although the current study was not designed to assess novel causes/mechanisms of SCA, it nevertheless provides at least one important insight into the role of relatively new SCA-predisposing clinical entities. Unexpectedly, ABiMVPS was the second most common etiology, behind IVF, observed in adult SCA survivors. This recently described and controversial clinical entity has been shown through post-mortem autopsy studies to play a previously underestimated role in arrhythmic SCD [8,29]. However, to our knowledge, the relative contribution of ABiMVPS has yet to be assessed or reported in any other population-based or referral cohort of SCA survivors.

As many of sentinel non-ischemic SCA survivors diagnosed with ABiMVPS were previously labelled as atypical LQTS or unexplained/IVF, ABiMVPS provides an important example as well as an impetus to carefully re-examine the clinical phenotypes of those individuals currently labelled as unexplained SCA/IVF for commonalities. In combination with further exploration of i) the greater use of provocation drug testing for cardiac channelopathies, coronary vasospasm, etc. [5] ii) the link between early repolarization and SCA/SCD [34], and iii) the unanticipated number of likely pathogenic/pathogenic variants in cardiomyopathy genes observed in SCA survivors/SCD victims with structurally normal hearts [24,35], we may find that the number of unexplained SCA/IVF cases will shrink dramatically over time.

5. Limitations

Although the number SCA survivors that remained unexplained following a comprehensive cardiovascular evaluation, including specialized studies and genetic testing, is similar to previous studies, the clear over-representation (i.e. LQTS, CPVT, etc.) and under-representation (i.e. HCM) of certain SCD-predisposing disorders underscores the strong referral bias present in this study. As mentioned previously, this inherent bias prevents generalization of this study's results beyond the current GHD-enriched tertiary medical center referral cohort.

Nevertheless, this study's largest limitation is simultaneously one of its greatest strengths. To our knowledge, this study represents one of the few contemporary examinations of non-ischemic SCA etiology undertaken in large referral cohort formally evaluated in the setting of a cardiovascular genomics clinic at a major tertiary medical center. Due to rare nature of both SCA-predisposing GHDs and unexplained SCA/IVF, this study is well positioned to address multiple questions, including the contribution of GHDs to SCA across the age-

spectrum, the identification of novel SCA etiologies, and the yield of genetic testing in unexplained SCA/IVF, not feasible in population-based studies. Indeed, through this referral cohort of individuals with a sentinel event of SCA, TKOS secondary to homozygous or compound heterozygous pathogenic variants in *TRDN*-encoded triadin was discovered as the root cause for a subset of children with previously genetically-elusive LQTS [9]. In addition, among a subset of female SCA survivors, the new entity of ABiMBPS emerged with its phenotypic tetrad: females with bileaflet mitral valve prolapse, abnormal looking T waves, and complex ventricular ectopy on ambulatory monitoring [8]. Interestingly, almost every one of these SCA survivors was referred to our Genetic Heart Rhythm Clinic with a referral diagnosis of atypical LQTS. Here, the very nature of our tertiary specialty center enabled an enrichment of these cases thereby enabling new syndromes to be discovered.

Lastly, as the patients that comprise this cohort of SCA survivors were referred over a ~18 year period, the clinical evaluation, including the selection and composition of genetic testing panels, was not, nor could it be, standardized. As such, the diagnostic and genetic yields reported in this study may be underestimated in comparison to national SCA registries with relatively standardized assessments such as CASPER [5,24].

6. Conclusion

Within a single-center referral population likely enriched for the presence of GHDs, the ability of a comprehensive cardiac evaluation, including genetic testing, to elucidate the root cause for the individual's sentinel event of SCA was highly age-dependent. Nevertheless, GHDs can present as sentinel SCA well into adulthood and merit consideration in all SCA survivors, regardless of age, with otherwise structurally normal hearts. Lastly, in the absence of a discernible GHD phenotype, the yield of genetic testing is predictably low. Further work is needed to define the appropriate role of genetic testing in unexplained SCA/IVF and determine if novel mechanisms/clinical entities, akin to ABiMVPS, underlie the large percentage of adult non-ischemic SCA survivors that remain stuck as cases of IVF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ARVC	arrhythmogenic right ventricular cardiomyopathy
ABiMVPS	arrhythmogenic bileaflet mitral valve prolapse syndrome
BrS	Brugada syndrome

CPVT	catecholaminergic polymorphic ventricular tachycardia
DCM	dilated cardiomyopathy
GHD	genetic heart disease
HCM	hypertrophic cardiomyopathy
IVF	idiopathic ventricular fibrillation
JWS	J-wave syndrome
LQTS	long QT syndrome
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SUDY	sudden unexplained death in the young

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Fig. 1.

Clinical diagnoses rendered in pediatric and adult sentinel sudden cardiac arrest survivors. Abbreviations: ABiMVPS, arrhythmogenic bileaflet mitral valve prolapse syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; and SCA, sudden cardiac arrest.

Fig. 2. Contribution of genetic heart diseases to non-ischemic, sentinel events of sudden cardiac arrest across the age spectrum. Abbreviations: GHD, genetic heart disease and IVF, idiopathic ventricular fibrillation.

Table 1

Demographics of the Mayo Clinic Genetic Heart Rhythm Clinic sentinel sudden cardiac arrest cohort.

	All SCA (n = 180)	Pediatric SCA (n = 53)	Adult SCA (n = 127)	p-Value^a
Sex (% female)	99 (55.0%)	25 (47.2%)	74 (58.3%)	0.2
Race (% Caucasian)	164 (91.1%)	46 (86.8%)	118 (92.9%)	0.2
Age at SCA (years)	28.0 ± 15.4	10.5 ± 5.8	35.3 ± 11.9	<0.0001
SCA circumstance				
Exertion/emotion	56 (31.1%)	27 (50.9%)	29 (22.8%)	0.0003
Rest	108 (60.0%)	19 (35.9%)	89 (70.1%)	<0.0001
Sleep	12 (6.7%)	5 (9.4%)	7 (5.5%)	0.5
Not known	4 (2.2%)	2 (3.8%)	2 (1.6%)	0.6
Public SCA	104 (57.8%)	32 (60.4%)	72 (56.7%)	0.7
Witnessed SCA	157 (87.2%)	46 (86.8%)	111 (87.4%)	1
Bystander CPR	142 (78.9%)	37 (69.8%)	105 (82.7%)	0.07
Genetic etiology ^b	71 (39.4%)	40 (75.5%)	31 (24.4%)	<0.0001

Abbreviations: CPR, cardiopulmonary resuscitation and SCA, sudden cardiac arrest.

^aDenotes comparison between pediatric and adult sudden cardiac arrest populations.

^bDefined as all genotype-positive and genotype-negative individuals diagnosed with a cardiac channelopathy (Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, SCN5A-mediated progressive cardiac conduction disease, or triadin knock-out syndrome), cardiomyopathy (arrhythmogenic cardiomyopathy, dilated cardiomyopathy, left ventricular non-compaction, hypertrophic cardiomyopathy, or restrictive cardiomyopathy), or other genetically-mediated sudden cardiac arrest-predisposing genetic condition (e.g. SCN5A-mediated idiopathic ventricular fibrillation) following comprehensive clinical evaluation/genetic testing.

Ultra-rare variants (MAF 0.005) found by commercial genetic testing in unexplained SCA survivors classified as IVF.

Table 2

Case #	Gene	Variant	gnomAD (MAF)	dbSNP ID	SIFT	PP2	ACMG Classification ^a	ACMG Evidence ^a	Ref.
MC0470	<i>SCN5A</i>	p.Glu30Gly	Absent	rs199473551	Deleterious	Probably damaging	VUS	PM2 and PP3	[15]
MC2274	<i>RYR2</i>	p.Val2933Gly	0.0001	rs550691734	Deleterious	Probably damaging	VUS	PP3	-
MC3210	<i>TC4P</i>	p.Pro141Ala	0.00003	rs45509691	Deleterious	Probably damaging	VUS	PP3	-
MC3574	<i>KCNH2</i>	p.Gly924Ala	0.000008	rs199473009	Tolerated	Probably damaging	VUS	-	[16, 17]
MC3654	<i>RYR2</i>	p.Glu243Lys	Absent	rs794728712	Tolerated	Probably damaging	Likely pathogenic (ii)	PS4, PM1, and PM2	[22]
MC4491	<i>AKAP9^b</i>	p.Arg421Gln	0.00002	rs864622705	Deleterious	Probably damaging	VUS	PP3	-
	<i>SCN10A^b</i>	p.Leu1186Met	0.00003	rs192493052	Deleterious	Probably damaging	VUS	PM1 and PP3	-
MC4742	<i>CACNB2^b</i>	p.Arg625Cys	0.00002	-	Deleterious	Probably damaging	VUS	PP3	[21]
MC4910	<i>DSP</i>	p.Glu1304Asp	0.00002	rs764189408	Tolerated	Benign	VUS	-	-
MC5854	<i>SCN5A</i>	p.Pro648Leu	0.00005	rs45609733	Tolerated	Benign	VUS	PM1	[18–20]
MC6170	<i>SCN5A</i>	p.Val146Met	0.0001	rs199473061	Deleterious	Benign	VUS	PM1	[15]
MC7290	<i>KCNH2</i>	p.Gly246Asp	Absent	-	Tolerated	Benign	VUS	PM2	-
	<i>RYR2</i>	p.Thr4535Met	Absent	rs756839134	Tolerated	Benign	VUS	PM1 and PM2	-
MC9691	<i>DES</i>	p.Alal35Gly	0.00002	-	Tolerated	Benign	VUS	-	-
	<i>PRKG2</i>	p.Glu484Gln	Absent	-	Tolerated	Benign	VUS	PM1 and PM2	-

Abbreviations: ACMG, American College of Medical Genetics and Genomics; gnomAD, genome aggregation database; MAF, minor allele frequency; ID, identifier, PM, pathogenic moderate; PP, pathogenic supporting; PP2, polymorphism phenotyping 2; PS, pathogenic strong; SCA, sudden cardiac arrest; SIFT, sorting intolerant from tolerant; and VUS, variant of uncertain significance.

^aDetails regarding rare variant adjudication framework, including specific evidence criteria and classification categories, employed in this study can be found in the 2015 ACMG variant classification and reporting guidelines [14].

^bDenotes genes with preliminary/questionable gene-disease association strength.