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ORIGINAL ARTICLE

The role of genetic testing in the prevention, diagnosis, and prognosis of sudden cardiac arrest in children

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Abstract

Background: Determining the pathogenesis of sudden cardiac arrest (SCA) in children is crucial for its management and prognosis. Our aim is to analyze the role of broad genetic testing in the prevention, diagnosis, and prognosis of SCA in Children.

Methods: ECG, 12-lead holter, exercise testing, cardiac imaging, familial study, and genetic testing were used to study 29 families, in whom a child experienced SCA.

Results: After a thorough clinical and genetic evaluation a positive diagnosis was reached in 24/29 (83%) families. Inherited channelopathies (long QT syndrome and catecholaminergic polymorphic ventricular tachycardia) were the most prevalent 20/29 (69%) diagnosis, followed by cardiomyopathy 3/29 (10%). Broad genetic testing was positive in 17/24 (71%) cases. Using the Mann–Whitney test, we found that genetic testing (effect size = 0.625, $p = 0.003$), ECG (effect size = 0.61, $p = 0.009$), and exercise test (effect size = 0.63, $p = 0.047$) had the highest yield in reaching the final diagnosis. Genetic testing was the only positive test available for five (17%) families. Among 155 family members evaluated through cascade screening, 73 (47%) had a positive clinical evaluation and 64 (41%) carried a pathologic mutation. During 6 ± 4.8 years of follow-up, 58% of the survived children experienced an arrhythmic event. Of nine family members who had an ICD implant for primary prevention, four experienced appropriate ICD shock.

Conclusions: The major causes of SCA among children are genetic etiology, and genetic testing has a high yield. Family screening has an additional role in both the diagnosis and preventing of SCA.

KEYWORDS
children, sudden cardiac arrest

1 | INTRODUCTION

The causes of sudden cardiac death (SCD) in children aged 1–18 years are ill defined especially when autopsy does not reveal the diagnosis, and in most studies deaths in children are described as part of young deaths up to 35–40 years of age.[1–4] Postmortem analysis often reveals structural cardiac abnormalities.[5,6] However, negative toxicology and a structurally and histologically normal heart

were found in up to 53% of these cases with a higher percentage among children as compared to young adults.[7,8] Inherited cardiac diseases such as channelopathies and cardiomyopathies are a possible cause of such autopsy negative SCD cases that may explain a significant number of these events.[2,9–11] Twenty-seven percent of children and young adults who suffer SCD are reported to have a family history of premature cardiac death.[12] All this emphasizes the importance of genetic etiology for SCD among children. Studies that examined several genes in persons younger than 40 years old who had experienced SCD have shown that genetic testing may identify a cardiovascular cause of death in up to 30% of these cases.[11,13–15] The exact yield of broad genetic testing in children experiencing SCD or sudden cardiac arrest (SCA) is unknown. Genetic testing can give an explanation for the sudden death, which is important for the mourning process of the families. The finding of an inherited genetic disorder also provides an opportunity to offer first-degree family members cascade screening. Identification of mutation carriers can reveal presymptomatic disease carrier and may save future lives.[14,16] Our primary aim was to define the causes of SCD or SCA in children from families who were referred to our inherited arrhythmia clinic. Second, we aimed to establish the diagnostic yield of cardiologic and broad genetic assessment of the proband and first-degree relatives.

2 | MATERIALS AND METHODS

We included 29 unrelated families who were consecutively referred to our inherited arrhythmia clinic at Rambam Health Care Campus (Haifa, Israel), a tertiary medical center in the north of Israel, during 2011–2017, in whom a child 18 years old or younger had SCA (aborted SCD) or non-aborted SCD. Inclusion criteria for aborted SCD were the occurrence of cardiac arrest requiring external defibrillation to restore sinus rhythm and a negative toxicology screen. In non-survivors, the death had to have occurred within 1 h of symptom onset or less than 24 h after the individual was last seen alive. In non-survivors, intoxication was ruled out by negative toxicology screen or negative autopsy and when not available by thorough inquiry of family members and close friends. The study design was approved by our institute's Ethics Committee. All the families underwent genetic counselling and have signed written informed consent.

We studied demographic variables, medical and family histories, previous cardiac tests if available, and SCD circumstances. Autopsy results were analyzed if available. In addition, we performed a cardiac investigation for the survived index case and first-degree family members in the clinic. The clinical workup for both the proband and each first-degree family member included: Family history, resting ECG, an exercise test, 12-lead holter, and transthoracic echocardiography. An electrophysiologist, an expert on inherited arrhythmia, interpreted the 12-lead holter information. At least 10 different calculations of the QT interval during stable heart rate (less than 10 beats per minute change during 2 min) in lead 2 or V5 were performed. Bruce protocol exercise test was performed in children aged 5 or older. The diagnoses of inherited primary arrhythmia syndromes and cardiomyopathies were made according to the proposed diagnostic criteria in the European Society of Cardiology guidelines.[17]

A genetic study was performed in families diagnosed or suspected of having genetic diseases such as cardiomyopathy or channelopathy, or when no definitive diagnosis was available based on DNA from the index case. If proband DNA was unavailable, DNA analysis was conducted on an affected relative. DNA was obtained from peripheral blood samples stored in EDTA. All patients underwent a consistent genetic panel of 343 genes linked to cardiomyopathy, channelopathy, cardiovascular disease, and SCD. The genes were sequenced using NGS illumine TrueSight Sequencing Panel. All coding exons and flanking intronic regions were sequenced. Variants of interest were Sanger verified and classified for pathogenicity using American College of Medical Genetics and Genomics guidelines.[18] The pathogenicity of the variants detected were cataloged according to their previous description, bioinformatics tools were used for in silico pathogenicity prediction and the degree of interspecies conservation of the residue and presence of the variant in public databases of the general population. In addition, before a mutation was considered probably pathogenic, it had to show coherence and familial co-segregation with the phenotype. Variants of unknown significance were considered negative.

In order to determine the diagnostic value of each test, we established a diagnostic score for test results that: (1) confused the final diagnosis (−1 point); (2) contributed to the final diagnosis by ruling out a specific diagnosis (1 point); (3) revealed a pathologic finding that contributed to the final diagnosis (2 points); and (4) contributed exclusively to the final diagnosis (3 points). In order to determine the diagnostic value of genetic testing we used the same scale for genetic results that (1) did not contribute to the final diagnosis (0 points); (2) confused the final diagnosis (−1 points); (3) supported the diagnosis (2 points); and contributed exclusively (the only modality) to final diagnosis (3 points).

Statistical analysis was performed using SPSS statistical software (version 20). Results are presented as mean ± SD, with $p < 0.05$ considered statistically significant. The Mann–Whitney *U* test was used for comparison of quantitative variables and the Chi-square or Fisher's exact test to determine proportions. We used Mann–Whitney test to find the most useful modality to reach a diagnosis.

3 | RESULTS

The study population included 29 index patients, mean age 11.1 ± 5 years (range 1 month–18 years): 17 (59%) males, QTC 478 ± 60 ms. Twelve (41%) children experienced syncope at age 8.7 ± 4 years before SCD and 9/12 children underwent clinical evaluation by their family physician. Five children were diagnosed with seizures, two with vasovagal syncope, and one with hypertrophic cardiomyopathy, although no therapy was recommended. In 15 (52%) children the malignant arrhythmia occurred during physical activity, in two (7%) while under emotion stress, and in 12 (41%) children while they were at rest (four of them while sleeping). Of the

index cases, 17 (59%) were deceased probands and 12 (41%) children survived. Postmortem analysis performed in three children revealed nonspecific findings. The baseline characteristics of the index cases are presented in Table 1. A definite or probable diagnosis was made in 24 (83%) families (Figure 1). Of the 167 family members, 155 (93%) underwent clinical evaluation in the clinic, with a clinically positive result in 73 (47%) of them. Channelopathies and especially congenital long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT) were the most common genetic etiologies. One patient (3%) was diagnosed with a nongenetic etiology, acute myocarditis (Figure 1).

Genetic testing was performed in 24 families. Five families were excluded from the genetic analysis (one child due to nongenetic diagnosis of acute myocarditis and four families for which no DNA was available). Among the 24 families (diagnosed with genetic etiology or no definitive diagnosis), genetic testing (consistent broad genetic panel of 343 genes) was performed. Genetic test was positive with identification of the probable causative mutation in 17 (71%) cases. The most frequently mutated genes were KCNH2, KCNQ1, and CASQ2 (Figure 2). The genetic variants that were identified are shown in Table 2. Cascade screening performed in 135 family members identified 64 (47%) affected individuals.

ECG, family screening, and genetic testing were the best modalities to find pathologic finding that contributed to the final diagnosis in 67%, 71%, and 71% of the evaluated families, respectively. Genetic testing, family screening, and exercise test were the exclusive modalities that enabled reaching the final diagnosis in 17%, 25%, and 18% of diagnosed families, respectively. In five families, genetic testing was the only modality that enabled reaching the final diagnosis. Autopsies were performed in 3/18 (17%) SCD victims. In two families, autopsy results confused the final diagnosis. The autopsy diagnosis was acute myocarditis, while the final diagnosis after examining family members and performing the genetic testing was CPVT and long QT. In univariate logistic regression, genetic testing ($p=0.0026$) and ECG ($p=0.025$) were statistically associated with reaching the final diagnosis. Family screening ($p=0.05$) had borderline association with reaching the final diagnosis. Using the Mann–Whitney test, we found that genetic testing (effect size=0.625, $p=0.003$), ECG (effect size=0.61, $p=0.009$), and exercise test (effect size=0.63, $p=0.047$) had the highest yield in reaching the final diagnosis among the families (Table 3).

TABLE 1 Baseline characteristics of the study population, $n=29$.

Variable	Mean ± SD or *n* (%)
Age, years	11 ± 5
Men	17 (59%)
Syncope pre SCD	12 (41%)
Family history of SCD	12 (41%)
SCD during exercise or excitement	17 (59%)
SCD occurred outdoor	17 (59%)
Aborted SCD	12 (41%)

Abbreviation: SCD, sudden cardiac death.

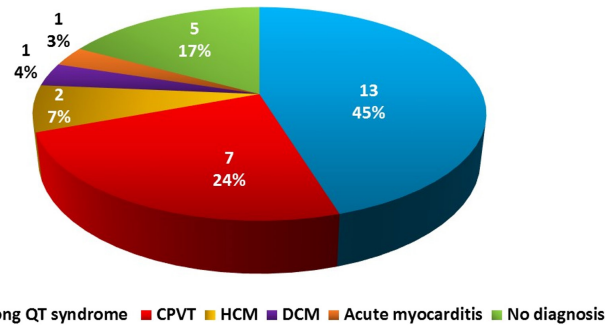

FIGURE 1 Final diagnosis after clinical and genetic evaluation in children experienced aborted and non-aborted SCD, at an inherited arrhythmia clinic $n=29$. CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome.

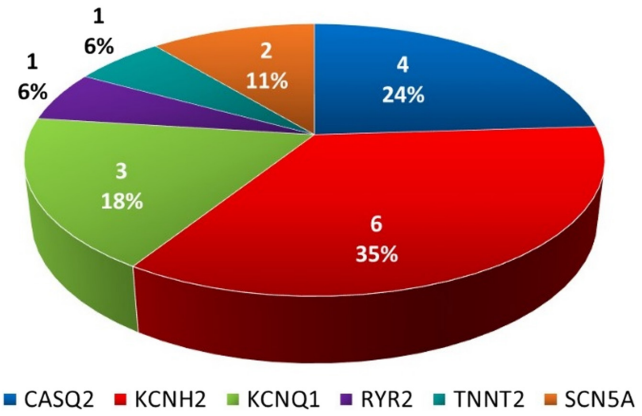

FIGURE 2 Genetic diagnosis in families with probable causative mutation, $n=17$.

The follow-up exams were during the mean follow-up period of 6.5 ± 2.8 years and no patients were lost during follow-up. Among 12 patients who survived the SCA, one boy diagnosed with acute myocarditis was medically treated without an implantable cardioverter-defibrillator (ICD) implantation. He did not experience SCA or syncope during long-term follow-up. Of the 11/12 (92%) surviving patients who underwent ICD implantation after the first event, eight were medically treated with beta blockers. During the follow-up, 7/12 (58%) patients experienced polymorphic ventricular tachycardia or ventricular fibrillation. The first event occurred between 1.2 month and 7 years, 2.4 ± 2.2 years after the first SCA. Five (42%) experienced a second arrhythmic event 3.3 ± 2.6 years after the first SCA and three (25%) a third arrhythmic event 5.3 ± 2.7 years after their SCA. All the events were polymorphic ventricular tachycardia or ventricular fibrillation and were successfully treated by the ICD. There were 13 lifesaving therapies in the all cohort (1.1 per patient). One child with anoxic brain damage related to SCA, died during the follow-up but not due to arrhythmia.

Among 73 clinically affected family members 64 (41%) carried a pathologic mutation found in the proband, 48 (66%) were followed

TABLE 2 The specific genetic variant that have been identified in SCD children cases, the disease causing, and the pathogenicity.

Gene	Variant	Disease	Pathogenicity
KCNQ1	P570L homozygous	LQT1	Likely pathogenic
KCNQ1	G589S homozygous	LQT1	Likely pathogenic
KCNH2	N629T heterozygous	LQT2	Likely pathogenic
KCNH2	A614V heterozygous	LQT2	Pathogenic
KCNH2	W568R heterozygous	LQT2	Likely pathogenic
KCNH2	E58G heterozygous	LQT2	Likely pathogenic
KCNH2	G914E heterozygous	LQT2	Likely pathogenic
KCNH2	T1146S heterozygous	LQT2	Likely pathogenic
SCN5A	V411M heterozygous	LQT3	Pathogenic
SCN5A	T370M heterozygous	LQT3	Likely pathogenic
CASQ2	D307H homozygous	CPVT2	Pathogenic
RYR2	T3866A heterozygous	CPVT1	Likely pathogenic
TNNT2	E163del heterozygous	HCM	Pathogenic

Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQT, long QT syndrome.

TABLE 3 The role of each test in reaching the final diagnosis by Mann–Whitney test.

Variable	Mean	SD	Median	Effect size	*p* Value
Electrocardiography	1.8	0.4	2	0.61	0.009
Family screening	1.83	1	2	0.26	N/A
Exercise test	2.1	0.6	2	0.63	0.047
12-lead holter	1.5	0.9	2	0.42	0.15
Echocardiography	1.3	0.45	1	0.196	N/A
Genetic testing	2.2	0.7	2	0.625	0.003

up in the clinic and medically treated. Nine (12%) family members underwent ICD implantation for primary prevention and four (44%) of them experienced appropriate ICD shock due to life-threatening ventricular arrhythmia. During the follow-up, one family member who had refused ICD experienced SCD and another family member died with an ICD most probably not due to cardiac cause. Among family members not followed in the clinic, five experienced SCD during the follow-up.

4 | DISCUSSION

In the present study, we evaluated the usefulness of clinical and broad genetic evaluation in a specialized inherited arrhythmia clinic on the diagnosis and prognosis of SCA and SCD in patients aged ≤18 and their family members. Our work shows that inherited heart diseases were found in 80% of these children. The major inherited diagnosis was long QT and CPVT (87% of the children were diagnosed with inherited heart disease). In previous clinicopathological studies in young SCD victims, structural heart diseases including cardiomyopathies were assumed to explain the majority of the cases.[19,20] Recent studies based on genetic testing have demonstrated higher rates of channelopathies (long QT syndrome and CPVT) among SCD patients, close to our rates especially among children.[5,21] These electrical diseases can only be diagnosed in survivors of aborted SCD in relative to SCD victims or through genetic testing.

Family screening had a diagnostic yield in 71% of families and was the only modality that enabled reaching the final diagnosis in seven families. In addition, family screening may reveal which relatives may be disease carriers, and consequently at risk of serious arrhythmias and SCD. In our study, the lives of at least four family members were saved. Thus, cardiological evaluation of surviving relatives of a child who suffered SCD seems to have high diagnostic yield and is strongly recommended even when the SCD victim can no longer be studied.

A broad genetic panel of 343 genes revealed pathogenic and probably pathogenic variants in 71% of families. In five families, genetic testing was the only modality that enabled the final diagnosis. Mainly due to de novo variant in the proband or only borderline clinical manifestation in family members. In previous studies up to 27 genes were studied in autopsy negative sudden death victims, the yields of the genetic testing were 11%–40%.[10,11,13,22–24] We assume that the relatively high positive rate of genetic testing in our study as compared to other studies was attributed to the broad genetic analysis and comprehensive clinical evaluation of the proband (if was available) and of family members.[21] Moreover, the young age of

SCD and SCA in our cohort (≤18 years old) may have played a role, as the yield of genetic testing in children is higher than the yield of young adults. In addition, our work emphasized the important role of exercise test in the clinical workup of children who have experienced SCA as well as in their family members. Exercise test is the only modality that can diagnose CPVT, which is an important etiology to SCD in children. The relatively high rate of autosomal recessive CPVT associated with homozygous mutation in CASQ2 gene in our families can be explained by a missense mutation in CASQ2, associated with CPVT, which has been described in Bedouin families in northern Israel.[25]

During long term follow up to 58% of patients with aborted SCD experienced at least one recurrent ventricular arrhythmia despite the optimal medical therapy with beta blockers. This emphasizes that children with inherited diseases who have experienced SCA are at high risk for recurrence of malignant arrhythmia, and thus ICD implantation is mandatory.

5 | CONCLUSIONS

Our study shows that in children aged ≤18 years, the major cause for SCD was inherited heart diseases, mainly electrical heart diseases (long QT and CPVT). Broad genetic testing combined with cardiologic clinical investigation of the proband if available, and family members (including exercise test) gave a high diagnostic yield. The finding of an inherited genetic disorder also provided an opportunity to offer family members cascade screening. Identification of mutation carriers can save future lives. Referral to a cardio genetics department is encouraged. Children with inherited diseases who have experienced SCA are at high risk for recurrence of malignant arrhythmia and ICD implantation is mandatory.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

ETHICS STATEMENT

This study was approved by our local IRB (institute's Ethics Committee).

PATIENT CONSENT STATEMENT

All the families underwent genetic counselling and have signed written informed consent.

CLINICAL TRIAL REGISTRATION

N/A.

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