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Comprehensive Diagnostic Work-Up for Uncovering the Causes of Sudden Cardiac Death: The Role of Family Members

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Abstract: Background: The aim of this study was to evaluate the performance of the diagnostic pathway proposed by the European Society of Cardiology (ESC) guidelines for identifying the underlying aetiology of sudden cardiac death (SCD) through the screening of first-degree family members of patients with SCD who either had a negative autopsy or no autopsy performed. Methods: To be eligible for enrolment, patients had to meet the following inclusion criteria: a family history of SCD in a first-degree relative under the age of 50 years; the SCD decedents must not have undergone an autopsy, or if an autopsy was performed, non-cardiac and structural cardiac causes must have been excluded. Patients underwent a comprehensive assessment, including the evaluation of family and medical history, electrocardiography (ECG) and ECG with high precordial leads, Holter ECG monitoring, echocardiography, cardiac magnetic resonance imaging, and exercise stress testing. A sodium channel blocker test (i.e., flecainide test) was performed when other clinical investigations were negative and the suspicion of Brugada syndrome was high. Results: Forty-one patients from 25 different families fulfilled the inclusion criteria and represented the final study cohort. After the comprehensive diagnostic work-up, a total of seven patients from five different families (5/25, 20%) were diagnosed with an inherited cardiac condition: two families with arrhythmogenic right ventricular cardiomyopathy, one with dilated cardiomyopathy, one with non-dilated left ventricular cardiomyopathy, and one with long QT syndrome. Conclusions: The comprehensive cardiologic work-up of relatives of mainly young SCD victims results in the diagnosis of inherited cardiac conditions in one-fifth of cases.

Keywords: sudden cardiac death; cardiomyopathy; channelopathy; genetic

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1. Introduction

Sudden cardiac death (SCD) is defined as an unexpected death due to cardiac causes, occurring within an hour of symptom onset in a person with or without known pre-existing heart disease [1]. The incidence of SCD varies with age, sex, and the presence of underlying cardiac conditions, being more prevalent in older adults and male sex [2–4].

Identifying an underlying inherited cardiac condition in patients who experience SCD is crucial for assessing the risk to family members and guiding tailored management [5,6].

Recently, the 2022 European Society of Cardiology (ESC) guidelines on the management of ventricular arrhythmias and SCD proposed a diagnostic approach for identifying the aetiology of SCD [1]. The autopsy and molecular genetic testing of the deceased are essential [7–9]. However, when an autopsy is not performed or yields negative results, a comprehensive assessment of first-degree family members is required to identify a possible inherited cardiac condition as the cause of SCD [1,6].

The aim of this study was to evaluate the performance of the diagnostic pathway proposed by the ESC guidelines for identifying the underlying aetiology of SCD through the screening of first-degree family members of patients with SCD who either had a negative autopsy or no autopsy performed.

2. Methods

An observational, longitudinal, retrospective cohort design was used. The study adheres to the principles of the Helsinki Declaration and received approval from the ethics committee of our institution. All patients provided written informed consent.

2.1. Eligibility Criteria

The cohort included consecutive patients with a family history of SCD in a first-degree relative under the age of 50 years, who were referred to a dedicated cardiomyopathy clinic (Inherited and Rare Cardiovascular Diseases Unit, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli," Monaldi Hospital, Naples, Italy) between January 2020 and December 2023.

To be eligible for enrolment, patients had to meet the following inclusion criteria: (1) a family history of SCD in a first-degree relative under the age of 50 years; (2) the SCD decedents should not have undergone an autopsy, or if an autopsy was performed, non-cardiac causes and structural cardiac causes must have been excluded.

Eligible patients were identified using multiple sources, including medical records and medical databases. The following keywords were used in the search strategy: sudden death, SCD, unexplained death.

2.2. Study Protocol and Data Collection

According to our protocol and in line with the ESC guidelines [1], each patient with a family history of SCD underwent a comprehensive assessment, including the evaluation of family history (e.g., age at SCD, circumstances of death), symptoms (e.g., syncope, palpitations), physical examination, 12-lead standard electrocardiography (ECG) and ECG with high precordial leads, Holter ECG monitoring, echocardiography, cardiac magnetic resonance (CMR), and exercise stress testing. A test with sodium channel blockers (i.e., flecainide test) was performed when other clinical investigations were negative and the suspicion of Brugada syndrome was high.

When a diagnosis of an inherited cardiac condition was made, patients underwent genetic testing. Genetic analysis was performed using a next-generation sequencing (NGS) panel containing 202 genes, including those commonly implicated in inherited cardiomyopathies. Extensive details of the NGS panel and procedure have been previously described [10]. Genetic testing was conducted after obtaining written informed consent.

2.3. Statistical Analysis

Normally distributed continuous variables are described as means ± standard deviation. Skewed data are described as medians (interquartile range [IQR]). Categorical variables are presented as numbers (percentage). All statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 27.0.

3. Results

Forty-one patients from 25 different families fulfilled the inclusion criteria and represented the final study cohort. The mean age was 36.5 ± 19.2 years, and 21 (51%) were

males. Eleven family members were the parents of the person who died suddenly, eleven were the children, and the remaining were siblings. Among the 25 families, autopsy was performed in 8 cases, while in the remaining 17 cases, it was not performed due to ethical or family reasons. The circumstances of death were unknown in 14 cases (56%). In the remaining cases, it occurred during sleep in seven (28%), rest in one (4%), or exercise in three cases (12%). In six families (24%), more than one SCD occurred under the age of 50.

Among the 41 patients examined, only 4 were symptomatic (unexplained syncope in 1 case and palpitations in 3 cases). All patients were in New York Heart Association (NYHA) class I, and no patients had chest pain or other symptoms. All the patients performed pedigree, physical examination, 12-lead and high-precordial leads ECG, echocardiography, and ECG Holter monitoring. In contrast, an exercise test was performed in 13 (32%) and CMR in 15 cases (37%). According to the underlying clinical suspicion, a flecainide test was recommended in 20 cases. However, only seven patients agreed to perform the test.

After the comprehensive diagnostic-work-up, a total of seven patients from five different families (5/25, 20%) were diagnosed with an inherited cardiac condition (Figure 1). All these patients performed molecular genetic testing. Three patients from two different families were diagnosed with arrhythmogenic right ventricular cardiomyopathy. Two patients carried a pathogenic variant in *DSG2* (c.2990del, p.Gly997Valfs*20, ACMG class V with the following fulfilled criteria: PS4; PS3; PP4; PSV1; PM2). One patient from a different family carried the same pathogenic variant in *DSG2* (c.2990del, p.Gly997Valfs*20, ACMG class V with the following fulfilled criteria: PS4; PS3; PP4; PSV1; and PM2) and a likely pathogenic variant in *RYR2* (c.12277G>C, p.Asp4093His, ACMG class IV with the following fulfilled criteria: PM1; PP2; PM2; and PP3). Two patients from the same family were diagnosed with non-dilated left ventricular cardiomyopathy. In these cases, genetic testing found no pathogenic or likely pathogenic variants in cardiomyopathy-associated genes. One patient was diagnosed with dilated cardiomyopathy, and genetic testing revealed a variant of uncertain significance in *TTN* (c.26761+2T>C, ACMG class III with the following fulfilled criteria: PP4; PM2; and PVS1). One patient was diagnosed with long QT syndrome with negative genetic testing.

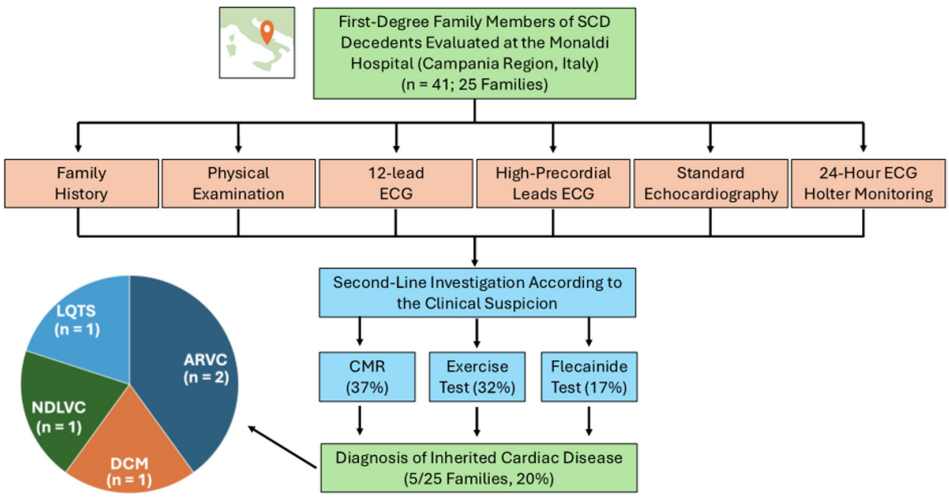

Figure 1. Consecutive first-degree family members of sudden cardiac death decedents were evaluated and a comprehensive assessment was performed, including evaluation of family history, electrocardiography (ECG) and ECG with high precordial leads, Holter ECG monitoring, and echocardiography. Cardiac magnetic resonance imaging, exercise stress testing, and the sodium channel blocker test (i.e., flecainide test) were performed as second-line investigations. A total of 7 patients from 5 different families (5/25, 20%) were diagnosed with an inherited cardiac condition: two families with arrhythmogenic right ventricular cardiomyopathy, one with dilated cardiomyopathy, one with non-dilated left ventricular cardiomyopathy, and one with long QT syndrome.

Moreover, all patients diagnosed with an inherited cardiac condition were family members of decedents who did not undergo an autopsy. In contrast, among the eight families in which an autopsy was performed, no family members were diagnosed with an inherited cardiac condition.

4. Discussion

This study evaluated the performance of the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD algorithm in assessing relatives of SCD decedents who did not undergo a negative autopsy or whose autopsy results were inconclusive. We found that after a comprehensive diagnostic work-up, the overall diagnostic yield was 20%.

Previous studies have investigated various diagnostic approaches for family members of SCD decedents. All study protocols included a similar initial diagnostic work-up, which involved gathering information on the circumstances of death, family and medical history, physical examination, ECG, echocardiography, and exercise testing [11–15]. For instance, Van der Werf et al. investigated 140 families with sudden unexplained death, diagnosing 33% of cases [11]; in that study, long QT syndrome was the most prevalent diagnosis. Similarly, Behr et al. investigated 109 first-degree family members of 32 people who died of sudden arrhythmic death syndrome (SADS), defined as decedents with normal cardiac pathological findings and negative toxicological tests [12]; the cardiological work-up included physical examination, ECG, echocardiography, and Holter monitoring, and 7 (22%) of the 32 families were found to have an inherited cardiac condition, with long QT syndrome being the most common, identified in four cases. Other diagnoses included non-structural cardiac electrophysiological disease, myotonic dystrophy, and hypertrophic cardiomyopathy [12]. Additionally, Tan et al. investigated 43 consecutive families with one or more sudden unexplained death victims who died before 40 years of age [13], and inherited cardiac disease was detected in 40% of cases (17/43 families); in this study, catecholaminergic polymorphic ventricular tachycardia and long QT syndrome were the most common diagnoses, and the likelihood of diagnosis increased when more family members were examined and when more than one sudden unexplained death occurred in the family.

The aforementioned studies yielded similar results, with long QT syndrome prevailing as the most common cardiac condition, while structural heart disease and Brugada syndrome were less common. These findings likely reflect the absence of CMR and sodium channel blocker testing in the initial diagnostic work-up. Subsequent studies explored the role of additional tests, such as high-lead ECG and signal-averaged ECG, CMR, and provocative testing [14,15]. As a result, the 2013 Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and Asia Pacific Heart Rhythm Society (APHRS) consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes first proposed these diagnostic tests as second-line investigations [16]. The impact of these modalities in increasing the diagnostic yield was subsequently investigated. Specifically, Papadakis et al. conducted a large study involving 911 relatives from 303 SADS families, who underwent an initial evaluation consisting of resting ECG using conventional and high right precordial leads, echocardiography, exercise testing, and 24 h ECG Holter monitoring [17]. When the initial diagnostic work-up did not identify an underlying inherited cardiac condition, 670 (74%) relatives underwent a sodium channel blocker test (i.e., ajmaline test) with conventional and high right precordial leads; they found that 28% of families tested positive on the provocative test and were diagnosed with Brugada syndrome. However, the possibility of false positives should be considered when interpreting the results of this test.

In our study, patients were primarily diagnosed with structural heart diseases, including arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, and non-dilated left ventricular cardiomyopathy. In one case, a diagnosis of long QT syndrome was made. Interestingly, no patient was diagnosed with Brugada syndrome. The discrep-

ancy in diagnostic yield and the higher prevalence of structural diseases in our study are likely related to the inclusion criteria and study protocol. Specifically, we investigated not only patients with negative autopsy results but also those who did not undergo an autopsy, which may explain the higher prevalence of structural heart disease in our cohort. In contrast, the absence of Brugada syndrome diagnoses is likely related to the study protocol [18].

Thus, our approach diverged slightly from that proposed by the 2022 ESC guidelines. Specifically, autopsies were performed in only a small proportion of patients, and molecular autopsies were not conducted. Additionally, sodium channel testing was not performed systematically. It was only conducted in patients with negative first-line investigations, including ECG, echocardiography, ECG Holter monitoring, exercise testing, and CMR, and with a high suspicion of Brugada syndrome (e.g., SCD during sleep or at rest). The decision not to perform the sodium channel blocker test systematically, but only in patients with high suspicion, was made to avoid a high false-positive rate. It has been observed that in patients with drug-induced Brugada syndrome without a spontaneous type 1 ECG pattern, the risk of life-threatening arrhythmias is low, with a median annual event rate of 0.5% over 5 years and 0.25% over 10 years [19].

Of clinical interest, among the eight families in which an autopsy was performed, no family members were diagnosed with an inherited cardiac condition. However, due to the small number of individuals in this subgroup, no definitive conclusions can be drawn.

Study Limitations

This study presents several limitations. First, this is a retrospective single-centre study with a relatively small sample size. Second, the diagnostic work-up was not completed in all the patients. The exercise test and CMR were performed in about one-third of patients, while a flecainide test was performed in about one-fifth. Third, genetic testing was performed only in patients fulfilling diagnostic criteria for inherited cardiac disease (i.e., cardiomyopathies or channelopathies). Thus, this study cannot evaluate the usefulness of genetic testing in diagnosing patients who performed a comprehensive diagnostic work-up and negative clinical results. Fourth, in most cases, autopsy was not performed. Fifth, molecular autopsy was not performed among patients with available autopsy. In conclusion, the diagnostic yield may be relatively underestimated due to the incomplete diagnostic work-up of several family members. Furthermore, the high proportion of siblings among the screened family members may have also impacted the results. Larger multicentre studies are required to validate these findings.

5. Conclusions

Comprehensive cardiologic and genetic examination of relatives of mainly young SCD victims results in the diagnosis of inherited cardiac conditions in one-fifth of cases. The diagnostic work-up proposed by the 2022 ESC guidelines on the management of ventricular arrhythmias and SCD facilitates the identification of family members with inherited cardiac conditions, highlighting the central role of family screening in diagnosis, especially in cases where autopsy is not performed and molecular autopsy is not available.

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Data Availability Statement: The data supporting the results of this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ARVC: arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECG, electrocardiography; LQTS, long QT syndrome; NDLVC, non-dilated left ventricular cardiomyopathy; SCD, sudden cardiac death.

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