ORIGINAL ARTICLE

Inherited Cardiovascular Diseases Cardiomyopathies – Cyprus Data

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Introduction

The term Inherited Cardiovascular Diseases (I.C.Ds) encompasses a group of cardiovascular diseases (cardiomyopathies, channelopathies, certain aortic diseases, and other syndromes) with a number of common characteristics: they have a genetic basis, a familial presentation, a heterogeneous clinical course and finally, they can all be associated with sudden cardiac death. These diseases have drawn a great deal of the scientific society's attention, during the present days, due to the fact that the sudden death (SD) of young people and athletes is evidently related to these inherited diseases.

The most common I.C.Ds are Hypertrophic Cardiomyopathy which occurs in 1 in 500 people, Arrhythmogenic Cardiomyopathy, which is observed at a frequency of 1 in 1000-5000 inhabitants, Dilated Cardiomyopathy observed in 4 per 10,000 inhabitants, Long QT syndrome observed in 1 per 2000 - 3000 inhabitants, Short QT syndrome observed in 2 per 10,000 inhabitants, Brugada syndrome observed in 1 per 5000 - 10,000 inhabitants, and Marfan syndrome observed at frequency of 1 per 10000 residents. According to this data, it is estimated that there are about 3000 people in Cyprus suffering from I.C.Ds.

The particularity of Cyprus in relation to Inherited Cardiovascular diseases

Cyprus, as an island, is considered a closed society. According to the phenomenon of closed societies, the incidence of hereditary diseases is higher than other countries with open societies. The particularity of Cyprus is due to the fact that it is located at the crossroads of three continents, Asia, Africa and Europe. Inevitably, it has been influenced by the various conquerors, not only culturally but also genetically, mainly as far as the various inherited diseases are concerned. The signs of visitors and conquerors are evident in the cultural, archaeological and other findings as well as in some inherited diseases observed in Cyprus.

Creation of a Reference and Study Centre for Inherited Cardiovascular Diseases in Cyprus.

Historical background, activities and current data.

Special Reference Centres have been set up in Europe and the USA for the purposes of referring people suspected or suffering from I.C.Ds. There was an urgent need to create in Cyprus a Reference Centre which on a systematic and organized basis will provide specialized services for the prevention, diagnosis and treatment of I.C.Ds. An important object of this centrewas also the cardiological control of athletes at secondary and tertiary level and the development of strategies for the prevention and treatment of I.C.Ds.across the Cypriot population. Simultaneously with the creation of an observatory for sudden death (SD), the reasons that caused a SD in the young people will be investigated and in case of I.C.Ds. the victim's family will be checked to identify other family members who suffer from I.C.Ds. and may be at risk. The main research stages for the investigation of I.C.Ds in the Cypriot population are the following:

2006: Creation of a Unitforstudying Inherited Cardiovascular Diseases in Cyprus

In 2006 an Inherited CardiovascularUnit was established at the General Hospital of Nicosia, which aimed to create a Reference and Study Centre for patients with I.C.Ds. Patients with I.C.Ds. from all over Cyprus were referred to the Unit for investigation.

2007: Research project of Arrhythmogenic Cardiomyopathy

In 2007, the Unit joined the European Research Study of Arrhythmogenic Cardiomyopathy in which a total of 23 countries participated (Project title: Multidisciplinary joint European research study on the clinical, pathological and genetic features of Arrhythmogenic Right Ventricular Cardiomyopathy Dysplasia-ARVC/D)[1].Based on this program and collaborations with other European centres, a large number of patients with ARVC/D in the Cypriot population were identified and investigated. The diagnosis of the disease was made based on specific diagnostic criteria[2], (Figure 1 and 2).

FIGURE 1

Echocardiogram of a patient with ARVC/D. Aneurysms are observed at the entrance site and at the top of the right ventricle which constitute a major criterion for the diagnosis of the disease. Finding 2 major criteria sets the diagnosis of ARVC/D.

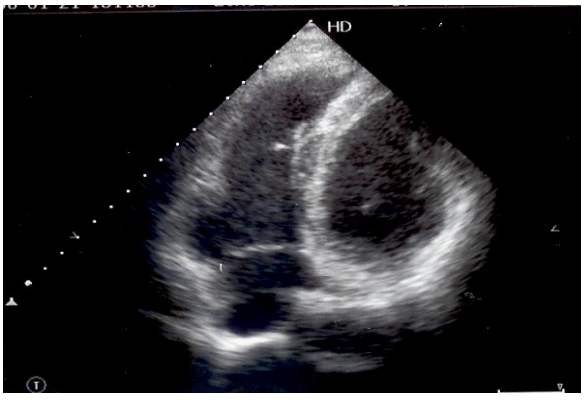
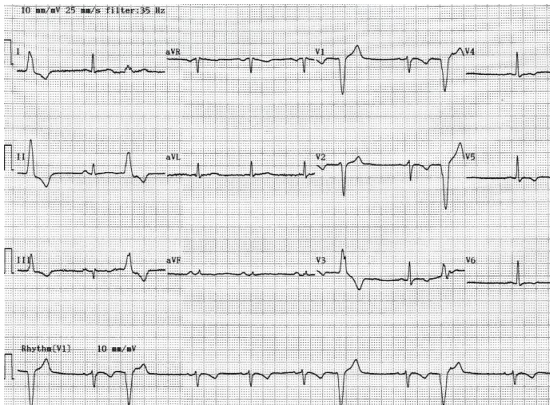


FIGURE 2

Electrocardiogram of a patient with ARVC/D. Negative T waves are observed in leads V1-V5 which are considered Major criteria for the diagnosis of ARVC/D. There are also several ventricular ectopic arising from right ventricle.



In collaboration with Heart Hospital London, University College London, under the guidance of cardiologist Nikos Protonotarios and Professors W.McKenna and P. Eliot, made the genetic investigation of all diagnosed cases with ARVC/D possible for first time.Up to day, 14 families with ARVC/D are being monitored with more than 60 patients. Through this research program, important announcements have been made in international cardiology conferences and several publications in medical journals [3,4,5,6] .

2008: Research program for the study of Hypertrophic Cardiomyopathy

In 2008 the Unit received a grant from the Cyprus Research Promotion Foundation and the General Secretariat of Technology and Research of the Ministry of Development of the Hellenic Republic, for the study of Hypertrophic Cardiomyopathy in the Cypriot and Greek population. (Project Title: Clinical Genetic Correlations in Greek and Cypriot Patients withHypertrophic Cardiomyopathy, genetic pool study

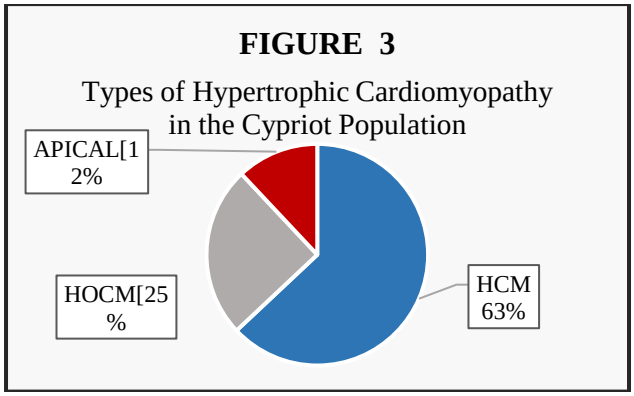
in Greece and Cyprus).

Starting from this program and with the cooperation of the Head of the program at Greece,Dr Aris Anastasakisat the 1st Cardiology Clinic of the University of Athens and now atOnassis Cardiac Surgery Center in Athens, collaboration with the Heart Hospital London, University College London, it was possible to identify and investigate a large number of families with Hypertrophic Cardiomyopathy in Cyprus[7,8].To date, more than 100 families with Hypertrophic Cardiomyopathy with more than 350 affected members are being monitored.

Of these patients, 70% are men and 30% are women. The type of cardiomyopathy is hypertrophic type (HCM) in 63% of cases, obstructive type (HOCM) in 25% and Apical type in 12% of cases (Figure 3). In 40% of the studied patients the cardiomyopathy has familial form and in 60% a sporadic form. A small number of patients with Non-CompactionCardiomyopathy were also monitored [9].

FIGURE 3

Types of Hypertrophic Cardiomyopathy in the Cypriot Population



2009: Research program for the study of Dilated Cardiomyopathy

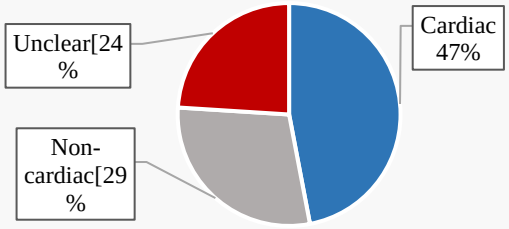
In 2009, in collaboration with the Cyprus Institute of Neurology and Genetics (I.N.G.), the genetic investigation of families with Dilated Cardiomyopathy (DC) was launched. Based on this cooperation, mutations of Lamin A/C cardiomyopathy were detected in a large family with many premature cardiac deaths in a young age[10]. Understanding the genetic background of this family, contributed to the understanding of the disease, early detection of complications, and the timely implantation of a cardiac defibrillator to prevent sudden death. Several other families with DC are being monitored, some of whom have undergone heart transplantation. Based on the collaboration with the I.N.G., a Genetic DNA Bank for I.C.Ds was established and genetic material was collected from patients and families with I.C.Ds.

2006 - 2016: Program for the investigation of the Sudden Deaths of Young People in the Cypriot population.

During the years 2006 – 2016, a Program for the investigation of sudden deaths cases of young people in the Cypriot population took place. During this period, 74 cases of SD in young Cypriot people were investigated. This study showed that 47% of SD cases were of cardiac origin, 29% were related to non-cardiac causes and 24% remained unclear (Figure 4).

FIGURE 4

Causes of Sudden Death of Youth in the Cypriot Population



Of the cardiac causes, 51% were attributed to cardiomyopathies, 17% to coronary artery disease, 9% to electrical syndromes and 23% to other heart causes(Figure 5).

Of the non-cardiac causes of SD, 38% were due to Pulmonary Embolism, 19% due to Cerebral Haemorrhage, 14% due to aortic aneurysm rupture and 29% due to other non-cardiac causes(Figure 6).

Data from the investigation of SD in the Cypriot population have been announced at conferences and have been published in medical journals [11,12,13,14].

FIGURE 5

Cardiac Cause of Sudden Death of Youth in the Cypriot Population

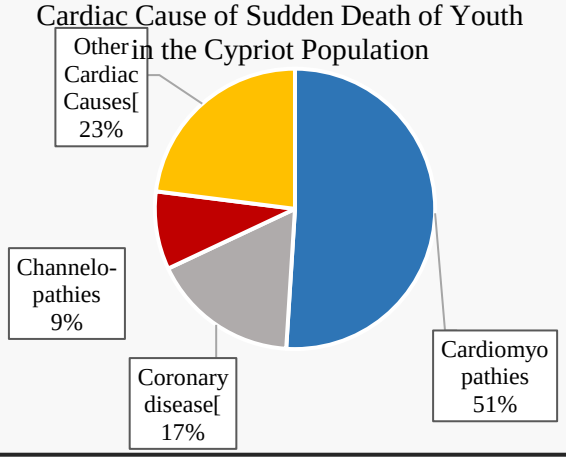
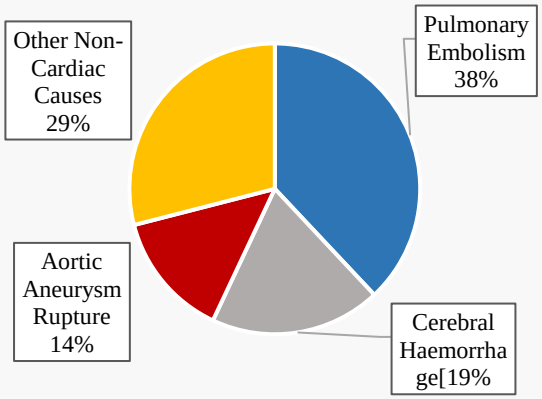


FIGURE 6

Non-Cardiac Causes of Sudden Death of Youth in the Cypriot Population



At the same time, research collaborations with Centres at United Kingdom and Greece continued in order to study the assessment of arrhythmic risk in patients with hypertrophic and arrhythmogenic cardiomyopathy (Project title: International External Validation Study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic risk assessment in genotyped families with arrhythmogenic right ventricular cardiomyopathy), as well as the contribution of genetic testing to the investigation of cases of SD,in the youngpopulation[13,14,15]

2006-2016: Creation of a DNA Genetic Bank forInherited Cardiovascular Diseases in Cyprus.

In collaboration with the Cyprus Institute of Neurology and Genetics (ING), the first phase of genetic processing is taking place, such as the extraction and storage of DNA. A Genetic Material Bank with genetic material from I.C.D. cases in the Cypriot population has already been created at the Institute, which includes genetic material from almost all known cases of I.C.Ds in Cyprus. The Bank also keeps DNA material from several cases of SD in young people. As it was mentioned before, genetic testing of patients with ARVC/Dhas already performed, after DNA samples were sent to the genetics laboratory at UCL in London as part of a European research project.

With the introduction of the Next Generation Sequencing method that allows simultaneous examination of many genes arose the possibility of completing molecular genetic testing of I.C.Ds in Cyprus. With the help of genetic testing, family trees and association maps, we can monitor the inheritance of a disease or other characteristics within a family, identify atypical forms and even asymptomatic carriers that cannot be detected by other clinical means and thus create a social protection network for the sudden death of young people and athletes in the Cypriot population.

2018: Establishment of the Cyprus Institute of Cardiomyopathiesand Other Inherited Cardiovascular Diseases.

In 2018, the Cyprus Institute of Cardiomyopathies and other Inherited Cardiovascular Diseases was established. The main objectives of the Institute were the investigation and management of patients with cardiomyopathies and other I.C.Ds in Cyprus and the raising of awareness in Cypriot people and Health Workers about I.C.Ds. In June 2019 and December 2022, Seminars for the prevention of SD in young people and athletes, wereorganised at the European University Cyprus. In 2020, a Book - Guide for the evaluation of ECG in young people and athletes has

been also issued by the Institute[16].

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