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Special article

Plan of Action for Inherited Cardiovascular Diseases: Synthesis of Recommendations and Action Algorithms

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ABSTRACT

The term inherited cardiovascular disease 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, can all be associated with sudden cardiac death. The present document summarizes some important concepts related to recent advances in sequencing techniques and understanding of the genetic bases of these diseases. We propose diagnostic algorithms and clinical practice recommendations and discuss controversial aspects of current clinical interest. We highlight the role of multidisciplinary referral units in the diagnosis and treatment of these conditions.

Protocolo de actuación en las cardiopatías familiares: síntesis de recomendaciones y algoritmos de actuación

Palabras clave:
Miocardiopatías
Canalopatías
Síndrome de Marfan
Muerte súbita

RESUMEN

Con el término cardiopatías familiares se designa un grupo de enfermedades cardiovasculares (miocardiopatías, canalopatías, algunas enfermedades aórticas y otros síndromes) que comparten una serie de características comunes: tienen una base genética, una presentación familiar, un curso clínico heterogéneo y, por último, todas pueden relacionarse con la muerte súbita. El presente documento recoge de forma resumida algunos conceptos importantes en relación con los avances recientes en las técnicas de secuenciación y el conocimiento de las bases genéticas de estas enfermedades. Se proponen algoritmos diagnósticos y recomendaciones prácticas y se debaten aspectos de interés clínico controvertidos y actuales. Se resalta el papel de las unidades de referencia multidisciplinares para diagnosticarlas y tratarlas.

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Abbreviations

HCM: hypertrophic cardiomyopathy
ICVD: inherited cardiovascular disease

INTRODUCTION

The term inherited cardiovascular diseases (ICVD) covers a group of cardiovascular diseases (cardiomyopathies, channelopathies, certain aortic diseases, and other syndromes) with several common characteristics:

1. They have a familial presentation. Thus, the relatives of affected people should be studied because they may have also inherited the disease. "When we treat a person with inherited cardiovascular disease, we do not just evaluate the patient, but the family as well".[1] Because families are studied, coordination with pediatric cardiology units is vital.
2. They have a genetic basis and can currently be diagnosed using genetic techniques. Although not all of the causal mutations of the ICVD have been identified, the percentage of mutations identified has increased in recent years, reaching greater than 50% for some cardiomyopathies and channelopathies, such as hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy, and long QT syndrome (Table 1).
3. They can cause sudden cardiac death, sometimes as the first presentation of the disease. Sudden cardiac death has a high social, economic, and media impact. The leading cause of sudden cardiac death of elderly individuals with coronary heart disease risk factors is ischemic heart disease, whereas ICVDs are frequent causes of sudden death in those younger than 35 years (both athletes and nonathletes).[7,8]

In recent years, various consensus documents and clinical guidelines have been published worldwide on the diagnosis and treatment of cardiomyopathies, channelopathies, and various aortic diseases with genetic origins. All agree on the need (with different recommendation and evidence levels) to study the relatives of affected patients, as well as to perform genetic studies (Table 2).

To diagnose and treat ICVDs, we also highlight here the creation of specialized referral units. These units should be multidisciplinary and maintain close links with other services and specialities.[2,9] However, in Spain, these referral units are unavailable in some communities, making it sometimes difficult to comply with many of the recommendations of these documents.

The present document has been created by the Working Group on Inherited Cardiovascular Disease of the Spanish Society of Cardiology (*Sociedad Española de Cardiología* [SEC]) in collaboration with the Working Group on the Aorta (from the Clinical Cardiology Section), the Working Group on Sports Cardiology, the Electrophysiology and Arrhythmias Section, the Heart Failure and Heart Transplant Section of the SEC, and the Spanish Society of Pediatric Cardiology and Congenital Heart Diseases. Moreover, the document has been reviewed by a group of Spanish and international experts (Appendix).

One of the aims of this document was to explain various aspects of the care of patients with ICVD in order to bridge the gap between Spanish clinical practice and the guidelines and recommendations.

The Spanish Ministry of Health has designated several referral units (*Centros, Servicios y Unidades de Referencia* in the Spanish National Health System) for the diagnosis and treatment of ICVD.[10] These referral units are essential for complex cases, namely, those with diagnostic and/or treatment difficulties, but we believe that the "way of working" of the ICVD units should be exported to all health care professionals (eg, cardiologists, internists, cardiovascular surgeons, geneticists, pediatricians, nurses, psychologists) who may be involved in the study and treatment of these conditions.

Additionally, we have paid special attention to certain aspects and terms due to their novelty or multidisciplinary characteristics. Finally, certain basic recommendations have been highlighted (Table 3), to be used as jumping-off points to further the understanding and treatment of these diseases.

Table 1
Percentage of Patients Whose Inherited Cardiovascular Disease Can Be Linked to a Causal Mutation

Inherited cardiovascular disease	Positive genetic studies*, %
Hypertrophic cardiomyopathy	40-70 (Elliott et al[2,3])
Dilated cardiomyopathy	30 (Elliott et al[3], Ackerman et al[4])
Restrictive cardiomyopathy	Unknown (Elliott et al[3], Ackerman et al[4])
Noncompaction cardiomyopathy	17-41 (Elliott et al[3], Ackerman et al[4])
Arrhythmogenic dysplasia/ cardiomyopathy	60 (Elliott et al[3], Ackerman et al[4])
Brugada syndrome	20-30 (Ackerman et al[4])
CPVT	60-70 (Ackerman et al[4])
Long QT syndrome	70-80 (Ackerman et al[4])
Short QT syndrome	Unknown (Ackerman et al[4])
Marfan syndrome	70-93 (Loeys et al[5])
Loeys-Dietz syndrome	Depends on the clinical/imaging evaluation (Arslan-Kirchner et al[6])

CPVT, catecholaminergic polymorphic ventricular tachycardia.
* Most of these percentages are based on genetic studies performed in few genes with the Sanger technique; these percentages are being improved by the current use of next-generation sequencing.

FAMILY HISTORY (FAMILY TREE OR PEDIGREE)

A family tree, genealogical tree, or medical pedigree is a graphical representation of the medical history and kinship of a family. With recent advances in genetic techniques and their increasingly widespread use, all physicians (or health care professionals) should be able to draw and interpret a family tree.

A detailed family tree with 3 generations should be created as part of the evaluation of patients with ICVD (Figure 1). Questions should be formulated to extract the relevant information on the cardiological history and symptoms suggesting a cardiac origin.[11,12]

Thus, it is important: *a*) to identify the index patient (or proband), that is, the first case evaluated in the family (can be alive or dead); *b*) record names, birthdates, and causes and ages of deaths (including sudden infant death), while always respecting the applicable data protection laws; *c*) to rule out the existence of consanguinity and to ask about the geographical origins of the family; *d*) to investigate symptoms, signs, complications, and treatments (eg, defibrillators, pacemakers, heart/kidney transplant) potentially related to the ICVD being studied, and *e*) to include all available documentation in the family study, including clinical history and previous electrocardiogram results. It is also crucial to locate any autopsy reports.

TYPES OF INHERITANCE

Most ICVD have an autosomal dominant mode of transmission, that is, a patient can transmit the disease to both males and