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Family Sudden Death Risk-Assessment Unit: Experience at the Valencian Community

Unidad de Valoración del Riesgo de Muerte Súbita Familiar: Experiencia en la Comunidad Valenciana

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ARTICLE INFORMATION

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ABSTRACT

The sudden death is defined as the unexpected death that occurs within an hour of the onset of symptoms. This type of death has a high social, media and economic impact. The first cause is of cardiac origin, and within this, the ischemic heart disease is the most frequent, but family heart diseases (channelopathies and cardiomyopathies) are more important in children and young people, where they represent the first cause of sudden cardiac death. These family heart diseases have a clear genetic substrate that justifies the indication of an adequate study of the relatives of the deceased. According to the data of the Spanish population of the 2013 census (46.7 million inhabitants) in the Valencian Community, which represents 10% of this population, it is estimated that there are 20.000 people with some potentially lethal heart disease. Given the importance and the social impact of sudden death of cardiac origin, and since the medical-legal autopsy has limitations to diagnose the underlying disease in these types of deaths, the most opportune strategy is the multidisciplinary approach, which is why in 2008, the Family Sudden Death and Family Heart Diseases Unit was created in this region.

RESUMEN

La muerte súbita se define como el fallecimiento inesperado que acontece antes de una hora desde el inicio de los síntomas, este tipo de muerte tiene un alto impacto social, mediático y económico. La primera causa es la de origen cardíaco y dentro de estas la cardiopatía isquémica es la más frecuente, pero las cardiopatías familiares (canalopatías y miocardiopatías) son porcentualmente más importantes en niños y jóvenes, donde representan la primera causa de muerte súbita cardíaca. Estas cardiopatías familiares tienen un claro sustrato genético que justifica la indicación de un adecuado estudio de los familiares de los fallecidos. De acuerdo a los datos de la población española del censo de 2013 (46,7 millones de habitantes) en la Comunidad Valenciana, que representa el 10% de esta población, se estima que residen 20000 personas con alguna cardiopatía familiar potencialmente letal.

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Dada la importancia y el impacto social de la muerte súbita de origen cardíaco, y puesto que la autopsia médico-legal tiene limitaciones para diagnosticar la enfermedad subyacente en este tipo de muertes, la estrategia más oportuna es el enfoque multidisciplinar, motivo por el cual en el año 2008 se creó la Unidad de Muerte Súbita Familiar y Cardiopatías Familiares en esta región.

INTRODUCTION

The sudden death (SD) is defined as the unexpected death that occurs before an hour from the onset of symptoms, such death has a high social, media and economic impact[1].

The first cause of SD is that of cardiac origin and within this, the ischemic heart disease is the most frequent. However, family heart diseases (channelopathies and cardiomyopathies) are more important in children and young people, where they represent the first cause of sudden cardiac death (SCD)[2] (**Figure 1**). Unlike the ischemic heart disease, family heart diseases have a clear genetic substrate that justifies the indication of an adequate study to the relatives of the deceased with an extension of the circle to a cascade study, according to the results in previous generations.

All family heart diseases, except the hypertrophic cardiomyopathy that has a prevalence of 1/500, have prevalence lower than 1/2.000-5.000, which fit the definition of rare disease. According to the Spanish population of the 2013 census (46.704.314 inhabitants) and the prevalence of these diseases, in our country, it is estimated that there are some 200.000 individuals with family heart diseases (**Figure 2**), who have been diagnosed and treated (a minority) or not (unaware of the disease and unprotected against adverse events)[3]. If the population of Valencia represents 10% of the Spanish population, it is estimated that in this independent community are living 20.000 inhabitants with some potentially fatal family disease.

Given the importance and social impact of the SD of cardiac origin and since the medical-legal autopsy in this type of death has limitations to diagnose the underlying disease, the most opportune strategy seems to be a multidisciplinary approach, a motive by the which in 2008 was created the Family Sudden Death and Family Heart Diseases Unit at the Valencian community.

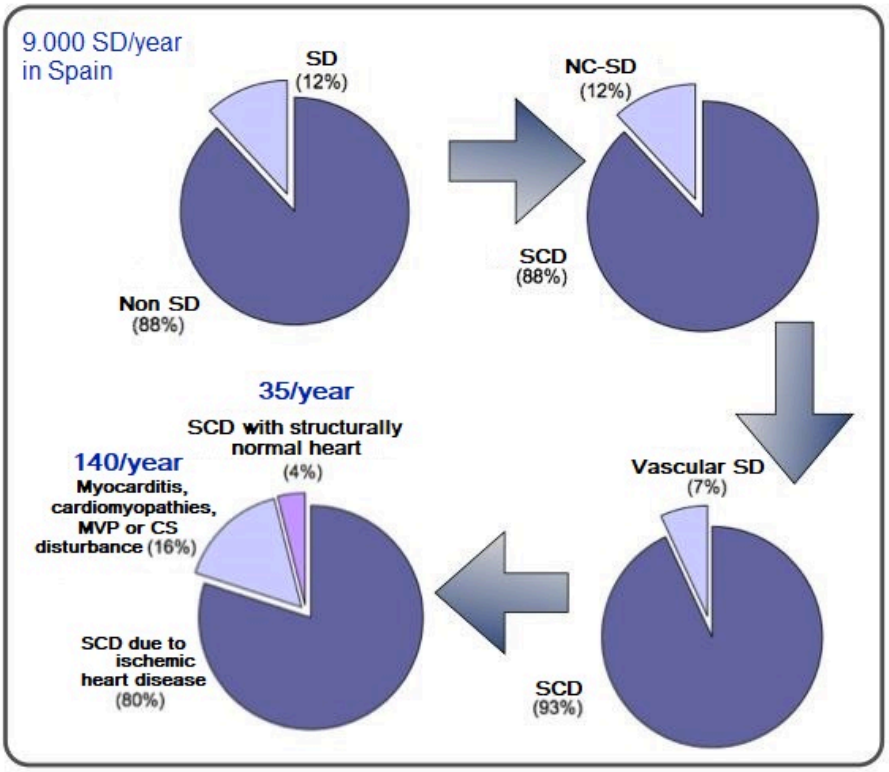

Figure 1. Scheme of the incidence of sudden death. CS, conduction system; MVP, mitral valve prolapse; NC non-cardiac; SD, sudden death; SCD, sudden cardiac death.

FUNCTIONAL FEATURES

This Unit is a pioneer in Spain in the multidisciplinary and multi-institutional approach of families affected by SCD, especially those related to family heart diseases of genetic origin. In fact, it is the first multidisciplinary unit in Spain with explicit agreement between the *Consellerías* of Health (which

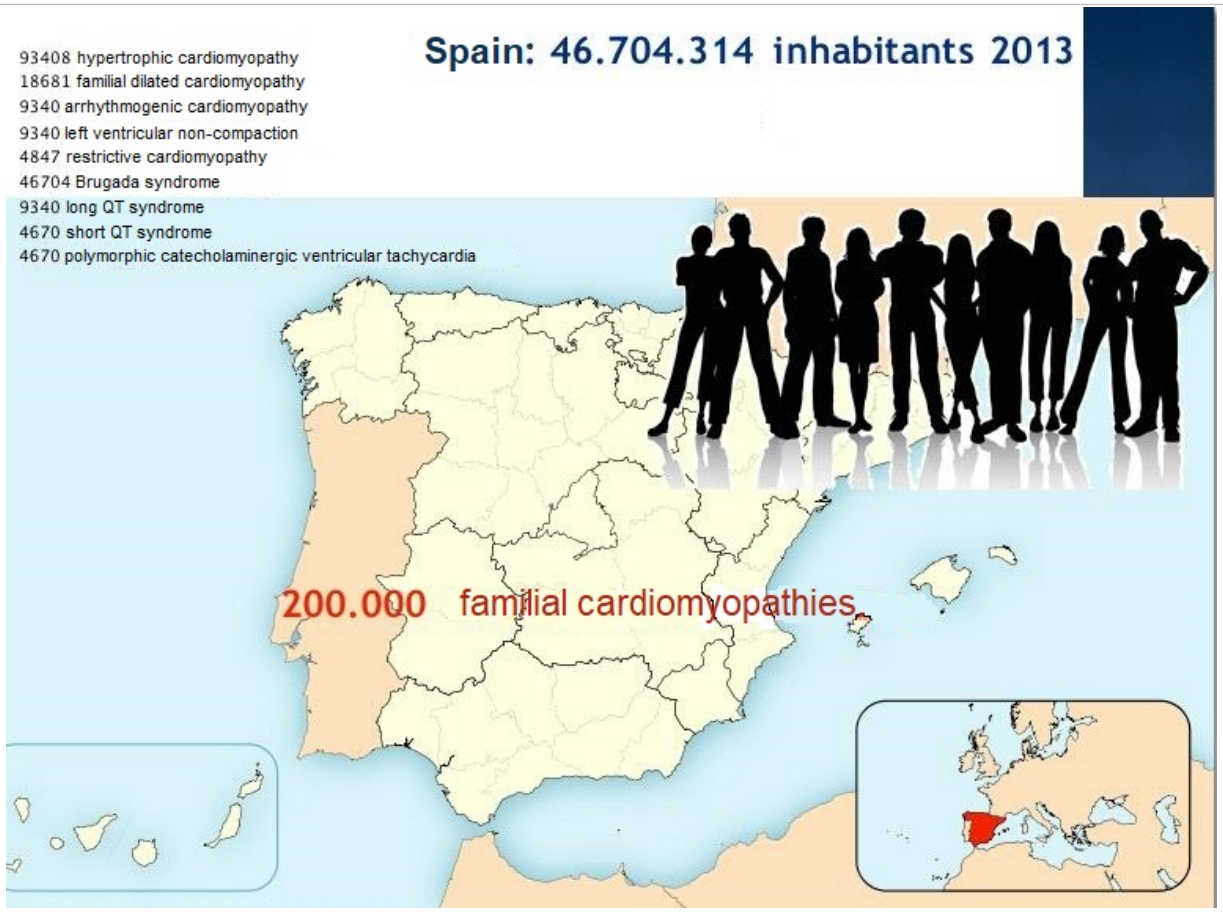

Figure 2. Epidemiological data from family heart diseases in Spain.

is responsible for clinicians and researchers) and Justice (who is responsible for forensic doctors and forensic pathologists), in a similar way as it was previously devised in the United Kingdom (Chapter Eight, NHS 2005)[4]. The Unit has a forensic subunit and a hospital subunit (**Figure 3**).

In the forensic subunit are carried out the judicial autopsies, which aim, among others, to identify the cause of death, provide morphological data and the collection of biological samples. Between 2008 and 2015, 618 cases of SCD have been studied. According to the results of the autopsies, these types of SD are classified into the following groups:

1. Structurally normal heart (where channelopathies are suspected).
2. Cardiomyopathies (hypertrophic, dilated, non-compacted, arrhythmogenic or non-determined).
3. Non-atheromatous thoracic aortic dissection (it includes bicuspid aorta).

The relatives of the deceased of these groups are called to the Institutes of Forensic Medicine, where they are informed the result of the autopsy and offered the possibility of a family hospital study (clinical subunit). The protocol is detailed in **figure 4**.

The sudden ischemic deaths are also studied in the autopsies that are performed in the Institutes of Legal Medicine. However, given the polygenic and multifactorial basis of atherosclerosis, the relatives of the deceased are not evaluated in the clinical subunit, but are advised to strictly control their cardiovascular risk factors and, in case of symptoms, to be referred to their cardiologist.

Circuits have been established for the flow of biological samples from the autopsy, that are to be studied within the health care or research field, or both; particularly, the *post mortem* plasma for the lipid profile study and those used for genetic studies in the context of family heart diseases of genetic origin.

Once the family member signs the consent, she/he is send to the clinical subunit where a study that includes clinical and genetic tests is developed.

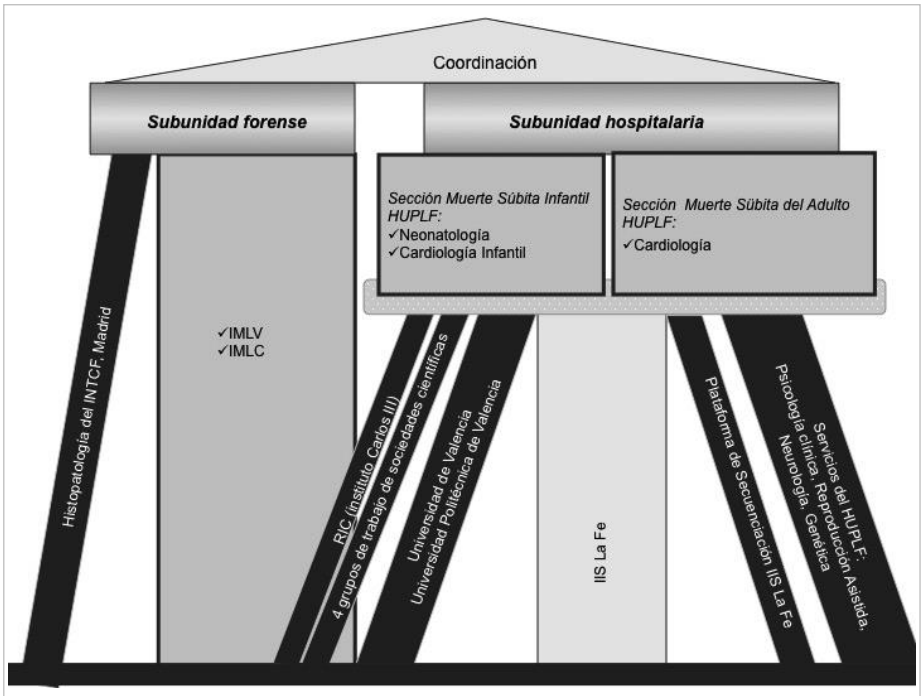

Figura 3. Flowchart of the Family Sudden Death Unit with the forensic subunit and the hospital subunit. In light gray, members of the Family Sudden Death Unit. In dark gray, usual external alliances.
Working groups of scientific societies: "Family Heart Diseases" of the Spanish Society of Cardiology, "Cardiomyopathies" of the European Society of Cardiology, "Sudden Infant Death" of the Spanish Association of Pediatrics and "Sudden Death" of the Spanish Society of Forensic Pathology.
HUPLF, Hospital Universitario y Politécnico La Fe; IMLC, Instituto de Medicina Legal de Castellón; IMLV, Instituto de Medicina Legal de Valencia; INTCF, Instituto Nacional de Toxicología y Ciencias Forenses; ISS, Instituto de Investigación Sanitaria; RIC, Red de Investigación Cardiovascular.

Until now, more than 25% of the members of families with family heart diseases have been diagnosed (clinical, genetic, or both) that has led to the changes in lifestyle (changes in sport activity), to start using drugs (mainly beta-blockers), to provide a list of medications to avoid (because they are potential triggers for arrhythmias in their disease), to maintain periodic reviews or even implant an automatic defibrillator (71 devices implanted in these families).

The most frequent diagnoses have been arrhythmogenic, hypertrophic, dilated and non-compacted cardiomyopathy; heart disease by laminopathy, long QT and Brugada syndromes, and polymorphic catecholaminergic ventricular tachycardia.

The recognition of these heart diseases has allowed clinical and genetic counseling to couples with gestational desire, depending on the information available in each case.

ACTION PROTOCOL

The protocol of this Unit, fed –largely– with previous experiences from the bibliography, includes studies for first degree relatives that extend in cascade, expanding the family tree, according to the results[1-8].

The clinical studies in relatives depend on the classification of the individual under study (*proband*) and, due to the great development of cardiogenetics in recent years –where public practical guidelines for conducting genetic testing in the context of these diseases[1-3] have been published– they are complemented by the results of genetic studies. These studies are performed on DNA extracted from the deceased's blood (obtained with the autopsy). If it is not available, a family with the same phenotype of the deceased is chosen; only if there is not blood sample available, the genetic studies are not performed.

CONFLICTS OF INTERESTS

None declared.

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Figure 4. Action flow of the Family Sudden Death Unit. The cardiological studies include: family tree, anamnesis, physical examination, electrocardiogram (ECG) and echocardiogram on the first visit. Additional explorations according to the data of the *proband*: Group 1: if the ECGs of the family members do not diagnose channelopathy: stress tests, holter, test of adrenaline and flecainide; Group 2: optional cardiac magnetic resonance, except in relatives of patients with arrhythmogenic cardiomyopathy where it is routine, holter if symptoms and in individuals with laminopa thy, hypertrophic cardiomyopathy or if they are relatives of the *probands* with arrhythmogenic cardiomyopathy, and Group 3: magnetic resonance or computerized tomography of optional aorta, other tests as suspicion of underlying disease. CCAA; autonomous communities; CF, family heart disease; MCA, arrhythmogenic cardiomyopathy; MCD, dilated cardiomyopathy; MCH, hypertrophic cardiomyopa thy; MCNC, left ventricular non-compaction; MS, sudden death.