

# Myocardial Disease As a Cause of Sudden Death in Children and Young Adults: Recognition and Preventative Strategies

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Myocardial diseases are primary disorders of the cardiac muscle, mainly of genetic origin.<sup>1</sup> Their presence within a single family and their heterogeneity, both in their mode of presentation and prognosis, means that they often have to be assessed in specialized centers in order to be treated. The initial mode of presentation can be sudden death.<sup>2</sup>

Most cases of sudden death in developed countries are due to coronary heart disease. However, the fundamental causes of sudden death in patients <35 years old are hereditary cardiovascular diseases and arrhythmias.<sup>3</sup> Although the incidence varies according to different series and ages, it is estimated that the figure is around 0.35-1.28/1000 people/year.<sup>2</sup> Given that most studies only focus on in-hospital deaths, these figures represent a decrease. The number of such cases increases with age and peaks at 60-65 years old.

Sudden death in young adults <35 years old is less frequent. Health professionals and health resource managers often view sudden death syndrome in numerical terms and, as such, it seems less important when compared to other more prevalent diseases. However, the unexpected death of a young adult is a devastating event, mainly occurring in people who, in addition to being considered healthy, are often keen sports practitioners.

The real incidence of sudden death in young adults has barely been documented in the literature. Furthermore, there are a group of deaths where the heart is morphologically and histologically normal but where death is caused by arrhythmias. In these cases the underlying disorder has a genetic cause, such as long QT syndrome. Some of these sudden deaths can be misdiagnosed due to attributing them to the consumption of toxic substances.

cardiomyopathies are among the most frequent causes of sudden death, and are primary myocardial diseases of genetic origin. The different cardiomyopathies, including hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy, among others, are recognized causes of sudden death. The diagnosis of these diseases at autopsy has obvious implications for the family members, since the most frequent inherited pattern is autosomal dominant. At present, very few health systems have implemented a protocol aimed at the resources necessary for research, identification, and prevention of these cases. The factors contributing to this event are, on the one hand, failure to recognize the condition due to diagnostic difficulty and, on the other, the lack of provision of resources.

It is important to highlight initiatives such as those taken by the Department of Health in the United Kingdom, which recently published the national plan for the prevention of sudden death (National Service Framework. Chapter 8: Arrhythmias and Sudden Cardiac Death).<sup>3</sup> For the first time, it has been recognized that there is a need to evaluate and refer patients and family members to centers where they can be assessed and comprehensive care given. Furthermore, it has also been recognized that the health system is responsible for guaranteeing that such measures are carried out effectively, and thus, acts as guide to what can be considered good clinical practice. Although this is still recent and has not been applied in practice, the recognition that both patients and members of a family with a history of sudden death and arrhythmias need specialized treatment represents a turning point. The plan identifies the vital points where the anatomic pathologist and the forensic doctor play a key role. Unfortunately, this is the starting point for many families. When a case is identified, the family needs support and also accurate clinical assessment. The findings, the tissue samples, and the availability of material for a possible genetic study play crucial roles in subsequent assessment of the family.

At this point it is worth reflecting on the epidemiological problem involved in these syndromes. With the development of genetics, entities such as unexplained

SEE ARTICLE ON PAGES 238-46

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ventricular hypertrophy are often included within the spectrum of hypertrophic cardiomyopathy, or else represent mitochondrial alterations or ventricular hypertrophy syndromes and alterations in the conduction system. Among the latter it is important to recall left ventricular hypertrophy syndrome associated with pre-excitation and based on alterations in genes that code for subunit  $\gamma 2$  of cyclic AMP-dependent protein kinase (PRKAG2).<sup>4</sup> This entity, which is morphologically identical to hypertrophic cardiomyopathy, is actually an alteration in glycogen metabolism.

In the last 2 decades progress has been made in identifying the risk markers associated with sudden death due to hypertrophic cardiomyopathy. In nonselected series, the annual risk is estimated to be around 1%. The predictive value of risk factors<sup>5</sup> related to an increased risk of a fatal event has also been studied. These risk factors are the presence of unexplained syncope, a family history of sudden death, the presence of nonsustained ventricular tachycardia during Holter monitoring, flat or hypotensive exercise blood pressure response,<sup>6</sup> a background of resuscitated cardiac arrest and severe ventricular hypertrophy. The presence of a left ventricular outflow tract gradient as well as the size of the left atrium are also related to a worse prognosis. Current guidelines recommend the implantation of a cardioverter defibrillator,<sup>7</sup> in the presence of 2 or more risk factors. In cases where there is only one risk factor, individualized treatment is very important.<sup>8,9</sup> The presence of nonsustained ventricular tachycardia is rare in young adults with hypertrophic cardiomyopathy, but when it does appear it has a very poor prognosis.<sup>8</sup>

Death occurs due to the triggering of malignant ventricular arrhythmias, either sustained ventricular tachycardia or ventricular fibrillation, which is more frequent in this age range. Several factors trigger fatal arrhythmic events and are often different in myocardial disease than in ion channel disease. However, it is important to recognize the pattern and symptoms related to the fatal event, such as syncope, especially if it is related to exercise, and palpitations having an impact on hemodynamics. These should be considered just as important as typical presentations of acute myocardial infarction.

Arrhythmogenic right ventricular cardiomyopathy of the is a recognized cause of sudden death. In Europe, especially in Italy, it is the leading cause of sudden death in athletes.<sup>10</sup> The pathological substratum is based on mutations of the genes that code for intracellular protein binding. Mechanical stress could play a key role in this entity by promoting apoptosis and the replacement of myocardial tissue by fibrofatty tissue.<sup>11</sup> Whereas the stage in which right ventricular dilatation and ventricular arrhythmias are obvious is relatively easy to diagnose, progression toward biventricular failure or onset with only microscopic changes can make it indistinguishable from cases of dilated cardiomyopathy or hearts with a normal structure, respectively. Thus, diagnosis during life is

difficult and is done using lower or greater probability criteria. It is important to point out that one of the main criteria is the presence of a family history of sudden death with histological proof of the diagnosis of arrhythmogenic right ventricular cardiomyopathy. Genetic diagnosis will unquestionably improve the assessment of this entity. Although there are no prospective series identifying possible risk markers, some studies conducted in patients with defibrillators, and arrhythmogenic right ventricular cardiomyopathy, have made it possible to identify potential risk markers.<sup>12</sup> These are syncope, left ventricular disorder, the presence of symptomatic ventricular arrhythmias and a family history of sudden death.<sup>12</sup>

A significant proportion of cases of sudden death can be prevented via early diagnosis and identification of high-risk individuals. The prophylactic implantation of cardioverter defibrillators is effective in preventing sudden death in these patients.

The present issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA contains a retrospective study,<sup>13</sup> which is both robust and highly illustrative of the cases of sudden death in a population of children and young adults <35 years old. This study is of special relevance, since there are major problems in the literature regarding series dealing with anatomical and clinical correlations.

The causative diseases are mainly hereditary ones or, at least, diseases where a genetic substratum is suspected.

Myocardial diseases deserve special attention, as they are particularly frequent in childhood and are one of the main causes of dilated cardiomyopathy. The causes of death related to acute or subacute myocarditis are progression to congestive heart failure, thromboembolic events and arrhythmias. The embolic events described in the series<sup>13</sup> are of particular interest. Indications for permanent or transitory anticoagulation therapy for the primary prevention of thromboembolic events in infancy are limited and differ from those recommended or practiced for similar diseases in adults. This is the case in severe dilatation of the left ventricle associated with ventricular dysfunction. Studies conducted in families with a high incidence of dilated cardiomyopathy have demonstrated that early presentation is often related to a viral infection episode. The theory of infection as triggering the expression of the dilated cardiomyopathy phenotype has been demonstrated in animal models.<sup>14</sup>

Although there is an inheritance pattern linked to chromosome X in some cardiomyopathies, the most frequent inheritance pattern is autosomal dominant. Thus, the disorder analyzed by sex should be proportional, but all the series described, including that of Morentin et al<sup>13</sup> report a greater percentage of males.

Arrhythmias related to exercise have caused controversy and the recommendations related to this are often not clinical, but medico-legal. These recommendations vary in different countries. Most of the cases of sudden death in young adults are not related to exercise. However, there are some cardiomyopathies in which exercise could play a

major triggering role. These include arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy with severe obstruction. There is no clear relationship between hypertrophic cardiomyopathy without obstruction and mild morphological characteristics and increased risk of sudden death due to exercise. It is important to systematically repeat the assessment of risk factors, particularly in adolescents and young adults, since in the majority of cases the most important changes occur during this period of life.

Sudden death is, thus, an infrequent cause of death in young people, but represents in itself an entity whose social impact is high and that demands multidisciplinary research and resources. Such resources are needed to optimize diagnostic certainty and establish accurate identification of high-risk individuals, as well as to indicate preventive therapies.

Forensic study should be regarded as the key to identifying an affected family and the starting point regarding assessing them. The availability of tissue, as well as appropriate informed consent regarding possible genetic study of such samples, is essential for any later study.<sup>15</sup> In order for this to be carried out effectively it is important to coordinate efforts and update the guidelines regarding the general approach to sudden death syndrome.

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