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Original Article

Cardiomyopathies as a Cause of Sudden Cardiac Death (SCD) in Egypt: Recognition and Preventive Strategies Needed

Open Access

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Abstract

This study aimed at evaluating the epidemiological characteristics and pathological features of different types of cardiomyopathies in Egypt, highlighting the role of the forensic pathologist in identifying cases of cardiomyopathies and initiating for their families a possible genetic study aiming at prevention of sudden death.

All cases with sudden cardiac death (SCD) due to cardiomyopathies during the period from the beginning of January 2010 until the end of December 2014 (5 years) were included in this study. All hearts underwent detailed gross and histological examination. Circumstances of death, medical history, and post-mortem pathological findings were thoroughly investigated.

Out of 535 cases of sudden cardiac death, there were 22 cases (4.1%) diagnosed as having cardiomyopathies; sudden death was their first presentation. Eighteen cases (81.8%) were male, with the 4th decade (11 cases, 50%) being the most affected age; severe physical activity and exertion were evident in death circumstances of 14 cases (63.6%); pathological evaluation revealed that hypertrophic cardiomyopathy was the most frequent type, being diagnosed in 10 cases (45%).

Cardiomyopathies are an infrequent cause of sudden cardiac death. Most deaths are in children and adults, so cases are of high social impact that demands multidisciplinary research and resources. In all cases of SCD, forensic autopsy should be done. Forensic study is the key to identifying an affected family and the starting point regarding assessing them.

Keywords: Cardiomyopathies, Sudden cardiac death (SCD), Forensic pathology.

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اعتلال عضلة القلب كسبب لموت القلب المفاجئ في مصر: ضرورة وضع الاستراتيجيات المطلوبة لتمييز الحالة والوقاية منها

المستخلص

هدفت هذه الدراسة إلى تقييم الخصائص الوبائية والمرضية لأنواع مختلفة من اعتلال (أمراض) عضلة القلب في مصر، وتسليط الضوء على دور الطبيب الشرعي في تحديد حالات اعتلال عضلة

القلب والشروع بإجراء دراسة جينية محتملة على أسر المتوفين تهدف إلى الوقاية من الموت المفاجئ.

شملت الدراسة جميع الحالات الواردة للموت القلبي المفاجئ (SCD) بسبب اعتلال عضلة القلب خلال الفترة من بداية يناير 2010 وحتى نهاية ديسمبر 2014 (5 سنوات). وخضعت كل القلوب إلى الفحص الإجمالي المفصل والفحص النسيجي. وتم التحقيق بملابسات الوفاة، والتاريخ الطبي، والموجودات المرضية ما بعد الوفاة بدقة.

كانت هناك 22 حالة (4.1٪) من أصل 535 حالة وفاة قلبية مفاجئة شخصت كاعتلال بعضلة القلب كان الموت المفاجئ أول عوارضها، كان من بينها ثمانية عشر حالة (81.8٪) من الذكور، وكان العمر الأكثر تضرراً لمن هم في العقد الرابع (11 حالة، 50٪). وكان من أهم ظروف الوفاة في 14 (63.6٪) حالة هو النشاط البدني الشديد والجهد الواضح. وكشف التقييم المرضي أن اعتلال عضلة القلب التضخمي كان هو النوع الأكثر شيوعاً مرضياً وجرى تشخيصه في 10 حالات وفاة (45٪).

عدت الدراسة أن اعتلال عضلة القلب سبباً معتاداً لموت القلب المفاجئ لأن معظم الوفيات من الأطفال والبالغين، وهذه الحالات لها تأثيرات اجتماعية عالية لذلك تتطلب بحوثاً ومصادر من عدة تخصصات. وينبغي أن يتم تشريح الجثة بشكل شرعي في جميع حالات موت القلب المفاجئ (SCD)، حيث إن دراسة هذه الحالات كحالات طب شرعي هو المفتاح لتحديد العائلات ذات الاستعداد للإصابة ونقطة البداية فيما يتعلق بتقييم حالتهم المرضية.

الكلمات المفتاحية: اعتلال العضلة القلبية ، موت القلب المفاجئ (SCD)، علم الأمراض الجنائي.

1. Introduction

Cardiomyopathies are primary disorders of cardiac muscle. They include dilated, hypertrophic, restrictive and arrhythmogenic right ventricular cardiomyopathy [1]. These are considered as a fundamental cause of cardiac death in children and adults [2]. Their initial mode of presentation could be sudden death [3]. It is a devastating event that happens in people who are often keen sport practitioners and considered very healthy [4].

Difficulty in picking-up affected survivors is an inherent risk for SCD. Cardiomyopathies are mainly hereditary or, at least, diseases where a genetic substratum is suspected [2]. Hence, the diagnosis of these diseases at autopsy and the identification of cardiomyopathies-related SCD would be a starting point for their families for detection of diseased members and prevention of sudden death.

Only few observational studies have assessed this problem all over the world [1-3]. To our knowledge, this is the first study in the Middle East that investigates the epidemiological characteristics of cardiomyopathies.

2. Materials and Methods

All cases with sudden cardiac death due to cardiomyopathies - during the period from the beginning of January 2010 till the end of December 2014 were included in this study.

Sudden cardiac death is defined as natural unexpected death witnessed within 6 hrs from the onset of symptoms. In cases of un-witnessed death, the definition is that the deceased had been seen in an apparently healthy condition 24 hours pre-mortem and all non-cardiac causes of death had been ruled out [5].

In Egypt, forensic autopsy is requested for sudden deaths that raise suspicion of criminal activity. Such deaths are referred to the Forensic Medicine Authority that is the part of the Ministry of Justice in Cairo, and their autopsied hearts are referred to the Forensic Pathology unit.

All autopsied hearts underwent detailed gross and histopathological examination based on recent guidelines developed by the Association for European Cardiovascular Pathology-for autopsy work in SCD [6]. Circumstances of death, medical history, and post-mortem histopathological findings were thoroughly correlated.

Histopathological sections where fibrois was suspected by H&E stain were selected for staining with the histochemical stain "Massons trichrome" to confirm the presence of fibrosis and determine its extent.

2.1 Statistical analysis

The collected data was organized, tabulated and statistically analyzed using SPSS software version 13. The dif-

ference in distribution of absolute frequency of SCD due to cardiomyopathy was calculated regarding age (different decades) and sex (male vs female) using Chi (χ^2) square test (Significance was adopted at $p < 0.05$).

To test the effect of death circumstances on sudden death due to cardiomyopathy, we used odds of event (event is death during evident factor and no event is death during rest) . Experiment group consists of cases with cardiomyopathy and control group is normal cases (considered positive when >1).

3. Results

The present study was conducted during the period from January 2010 to December 2014 (5 years). Our results revealed that out of 535 cases of SCD, only 22 cases (4.1%) were diagnosed as cardiomyopathies-related SCD (Table-1).

Table 1- *Causes of Sudden Cardiac Death (SCD) in Egypt during January 2010-December 2014*

Causes of SCD	No. of Cases	%
Coronary atherosclerosis	420	78.5%
Myocarditis	42	7.8%
Chronic valvular disease	22	4.11%
Cardiomyopathies	22	4.11%
Pure hypertensive heart disease	15	2. 8%
Aortic dissection	2	0. 37%
Ischemic heart disease with normal coronaries	12	2.24%
Total	535	100%

3.1 Epidemiological and Demographic Data

Of the 22 cases of death due to cardiomyopathies, 18 (81.8%) were male (9 of them had hypertrophic cardiomyopathy) and 4 cases (18.2%) were female. Male to female ratio was 4.5:1 with a significant increase in incidence in males than females ($p < 0.001$).

The age ranged from 1st decade till 5th decade, with a significant increase in incidence at the 4th decade (11 cases, 50%) ($p < 0.001$).

3.2 Types of cardiomyopathies observed in our study

Analysis of histopathological assessment showed that hypertrophic cardiomyopathy was the most frequent type; being diagnosed in 10 cases (45%), followed by dilated cardiomyopathy in 5 cases (23%), restrictive cardiomyopathy in 4 cases (18%) and arrhythmogenic right ventricular cardiomyopathy in 3 cases (14%).

3.3 Medical history and death circumstances

SD was the first presentation of cardiomyopathy in all studied cases. Co-incidental morbidities were reported in 3 cases; 2 cases with restrictive cardiomyopathy had received medical care for embolic manifestations and 1 case with congenital hypertrophic cardiomyopathy presented bilateral congenital cataract. Six cases (27%) had history of prodromal symptoms, mainly chest pain.

With regard to death circumstances, severe physical activity and exertion as arrhythmia triggering factors were reported prior to death in 14 cases (63.6%); in 11 cases, death occurred during struggle while in the other 3 cases, death occurred during strenuous physical activities. In 4 cases, death was not witnessed and happened at home, probably while sleeping. In another 4 cases, death occurred in hospital. Therefore odds of event = 14/8 = 1.75 (> 1) indicating that severe physical activity and exertion is positively associated with sudden death in cardiomyopathies (Table-2).

3.4 Pathological findings

Characteristic findings of hypertrophic cardiomyopathy were present in 9 cases; hypertrophy of both septum and anterior wall of the left ventricle (type III) was detected in 7 cases, while diffuse thickening of the septum without involvement of the free wall of ventricle (type II) was evident in 2 cases.

The wall thickness of interventricular septum ranged between 2.5 and 3.5 cm (mean 2.88 cm), and the left ven-

Table 2- *Death circumstances in cases of cardiomyopathies*

Cardiomyopathies	Severe physical activity and exertion*	Home	Hospital	Total
Hypertrophic	9	-	1	10
Dilated	-	2	3	5
Restrictive	2	2	-	4
Arrhythmogenic	3	-	-	3
Total	14	4	4	22

* *Severe physical activity and exertion are evident in death circumstances of cases with cardiomyopathy. Odds of event =14/8 =1.75 (>1) which means there is a higher chance of dying during severe physical activity and exertion than during rest.*

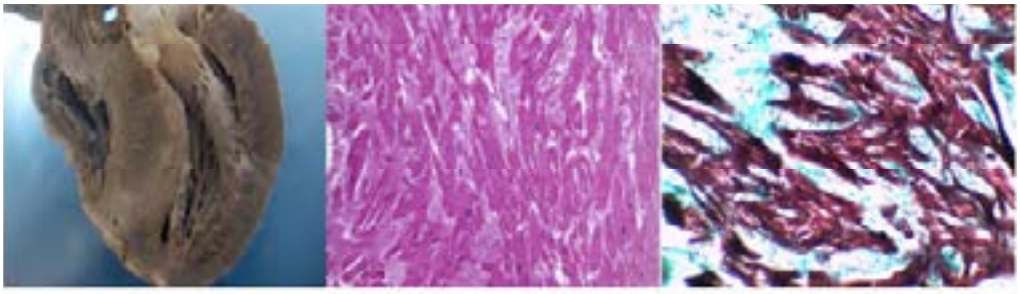

Figure 1- *Hypertrophic cardiomyopathy:*
Right: Longitudinal cut of the heart showing asymmetric septal hypertrophy and banana-shaped left ventricle (early stage) .
Middle: Photomicrograph showing hypertrophied myocytes, myofiber disarray and interstitial fibrosis (H&E, 40X).
Left: Photomicrograph (Masson-trichrome stain, 40X).

tricular wall thickness ranged between 1.4 and 1.7 cm (mean 1.55 cm), with a ratio ranging between 1.4:1 and 2:1. Banana shaped ventricle (early stage) was present in 8 cases while only 1 case showed ventricular remodeling (late stage). Microscopically, the myocardium of these cases showed myocyte hypertrophy and disarray with interstitial fibrosis and thick interstitial blood vessels, all of which are diagnostic lesions of hypertrophic cardiomyopathy (Figure-1).

One case, a female infant aged 4-months, was diagnosed with congenital hypertrophic cadiomyopathy. She had a clinical history of bilateral congenital cataract and delayed developmental milestones. She died suddenly while operating for her cataract. Grossly, her heart was hypertrophied. Microscopically, the myocardium showed myocyte hypertrophy with myofibrillar disarray and vacuolated myocytes (myofibrolysis). This constellation of findings suggested the diagnosis of Sengers syndrome.

All 5 cases that had dilated cardiomyopathy showed an increase in heart weight and reduced ventricular wall thickness with obvious ventricular chamber dilatation. Microscopically, the myocardium of these cases showed areas of interstitial fibrosis in some sections; focal lymphocytic

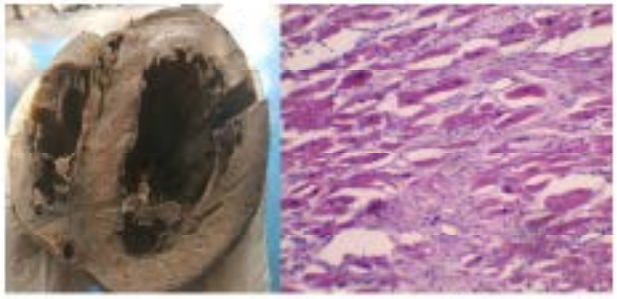

Figure 2- *Dilated cardiomyopathy:*
Right: Transverse cut showing dilated cavity of both ventricles.
Left: Photomicrograph showing myocyte attenuation, interstitial fibrosis and interstitial T-lymphocytes (H&E, 200X).

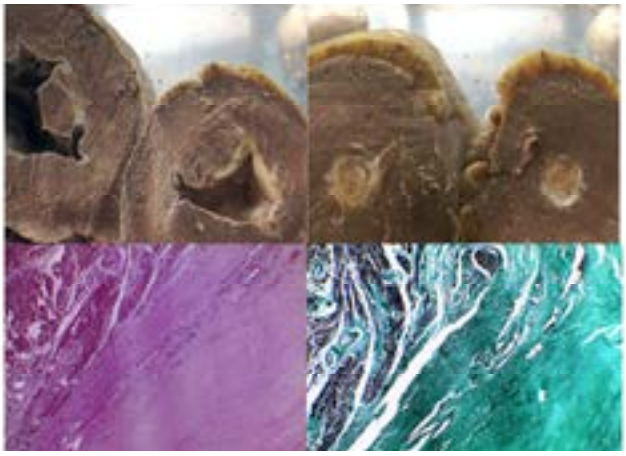

Figure 3- *Restrictive cardiomyopathy, (Endo-Myocardial Fibrosis):*
Top Right: Transverse section of the heart showing very thick fibrosed endocardium.
Top Left: Transverse section at the apex showing obliterated apex with fibrosis and calcifications.
Bottom right: Photomicrograph showing very thick fibrosed endocardium (H&E, 40X).
Bottom left: Photomicrograph, (massons-trichrome, 40X).

infiltrations were present in two cases (Figure-2).

Of the 4 cases diagnosed as restrictive cardiomyopathy, 2 were diagnosed as tropical endomyocardial fibrosis (EMF). Grossly, there was stiff myocardium and thick fibrosed endocardium till the level of A-V valves at both left and right ventricles, with obliterated apex by fibrosis and calcifications (Figure-3). In the other 2 cases – being diagnosed as Loffler's carditis - there were scattered whitish areas of endocardium. Microscopically, fibrosis was confirmed in suspected areas, with focal eosinophilic infiltrations being characteristically present in cases with Loffler's carditis (Figure-4).

Among the 3 cases that had arrythmogenic right ventricular cardiomyopathy, the right ventricle was solely affected in 2 cases, and both ventricles were affected in the third one. Grossly, the wall of right ventricle was very thin;

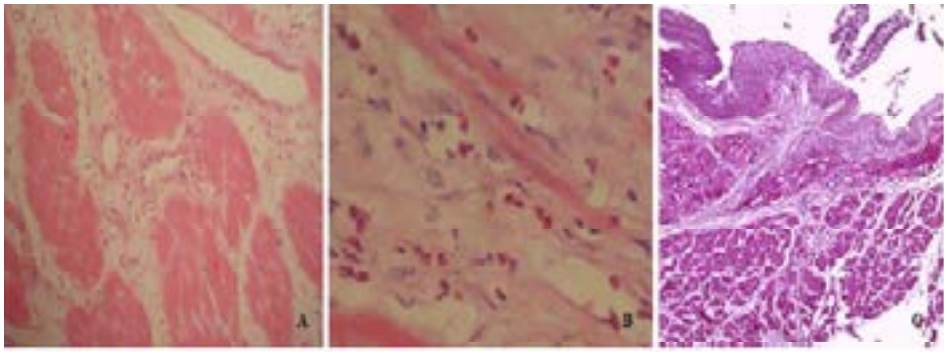

Figure 4- *Loffler's syndrome (Restrictive cardiomyopathy): A: Eosinophilic infiltrate at the myocardium (H&E, 200X). B: Eosinophilic infiltrate at the myocardium (H&E, 400X). C: Endocardial fibrosis in Loffler's syndrome (H&E, 200X).*

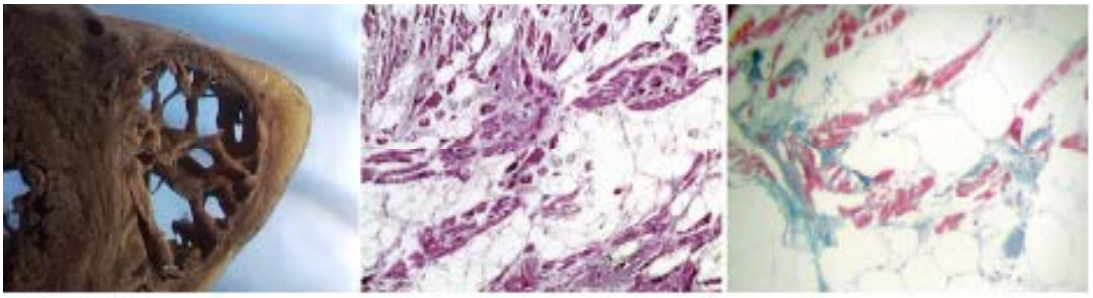

Figure 5- *Arrhythmogenic right ventricular cardiomyopathy:*
Right: Transverse section of the heart showing very thin wall of the right ventricle.
Middle: Photomicrograph showing fibro-fatty replacement of the myocardium(H&E, 200X).
Left: Photomicrograph, Massons- trichrome stain, 20X.

thickness was 0.1 cm (normal; 0.3 cm) and in some areas there was complete absence of the wall, with fat encroaching the trabeculae. In the case where the left ventricle was affected, there were pale areas (subepicardial, posterolateral wall) and scattered white patches. Microscopically, all cases were of the fibrolipomatous type, where the myocardium of the right ventricle showed large areas of fat cells in-between myocyte, appearing randomly "moth-eaten", with areas of fibrosis (Figure-5). In the case with biventricular involvement, left ventricle showed areas with fat infiltrations (sub-epicardial in-between myocytes) interstitial fibrosis and patches of fibrosis. More detailed microscopic investigations revealed the characteristic myocytic changes in the form of myocyte vaculations and nuclear attenuation.

4. Discussion

To our knowledge, the present study is the first report about cardiomyopathies as a cause of sudden cardiac death in Egypt. This may have important implications in planning strategies for prevention.

As reported in the presented autopsy series during the study period, it was found that the contribution of cardiomyopathies among other causes of sudden cardiac death is low (4.1%). Their actual incidence among survivors might be underestimated. Since all deaths were sudden, forensic pathology studies served as the only source of documentation of these cases.

The present study revealed that the incidence of SCD due to cardiomyopathies in Egypt is within the range described in other studies [7-9] while it is lower than others reported, ranging from 8 to 17% [10, 11]; but the comparison has to be made with considerable caution, as there is a wide spectrum of autopsy rates in different countries.

The first presentation of these diseases was the sudden death thereby making it dangerous and risky for carriers of these diseases. In a previous study [7], few cases with hypertrophic cardiomyopathy were diagnosed before death, but sudden death was the first presentation in the majority of the cases.

The risk of SCD was significantly higher in males and adults compared to females and children, respectively, corresponding to previous studies done on different types of cardiomyopathies [7, 12-14]. The natural history of the studied group showed that cardiomyopathies (specifically hypertrophic cardiomyopathy) are clinically silent until they are presented by SCD in adolescence. Hence, in order to prevent cardiomyopathies-related SCD, efforts should focus specifically on adult male relatives of the succumbed person.

There are geographical variations among types of cardiomyopathies: hypertrophic cardiomyopathy is especially frequent in North America, arrhythmogenic cardiomyopathy is more prevalent in Southern Europe [7] and restrictive cardiomyopathy is the most prevalent in tropical and subtropical countries in Africa, Asia, and South America [2]. According to the present study, hypertrophic cardiomyopathy is the most prevalent type in Egypt.

Arrhythmogenic cardiomyopathy is a relatively new and rare cardiac problem, previously it was considered to be endemic disease in North East Italy but now it is well recognized in different countries with no available data about its prevalence [15]. The present study has revealed its presence in Egypt; its diagnosis should be suspected in young adults with sudden cardiac death.

This study also revealed the presence of the primary type of restrictive cardiomyopathy in Egypt (18.18%), although it is considered the least common of the cardiomyopathic disorders in Western countries [16]. This rare disease has not been previously discussed or written about, since it is mainly a Sub-Saharan medical problem in Africa. According to the medical literature, the pathologist Jack N. P. Davies was the first to identify endomyocardial fibrosis (EMF) in 1947 in Uganda. Reports about that disease came from other parts of tropical Africa, South America and South Asia. It accounts for 20% of cardiac patients referred for echocardiography in Kampala, Uganda [17].

It is important to mention that the present study has also documented a case of “Sengers’ syndrome” reported by the

American heart association as a rare disease with congenital hypertrophic cardiomyopathy associated with bilateral cataract. This syndrome is an autosomal recessive condition characterized by congenital cataract, hypertrophic cardiomyopathy, skeletal myopathy and lactic acidosis. Mutations in the acylglycerol kinase (AGK) gene have been recently described as the cause of this syndrome in nine families [18]. The possibility of Sengers syndrome should be kept in mind while dealing with the cases of bilateral congenital cataract, hypertrophic cardiomyopathy or both.

Death in these diseases occurs due to lethal arrhythmias in a vulnerable myocardium [7]. Exercise and struggle which carry severe physical activity and exertion were evident in death circumstances of cases with cardiomyopathies especially hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy and restrictive cardiomyopathy. Severe physical activity and exertion are considered as a triggering factor for arrhythmia in cardiomyopathies [7, 12, 19-22]. Thus, vigorous activities should be contraindicated in young males affected with these diseases.

Cases of death at home lack the complete circumstances of death, whether death occurred at rest affected by an internal trigger of arrhythmia resulting from an increased response to intrinsic adrenergic hormones [23] or it occurred due to stress at the loss of a close person, loss of self-esteem, fear of personal danger or threat [24-25].

Pathological examinations in this study revealed that in 2 cases of dilated cardiomyopathy there were focal lymphocytic infiltrations confirming that the cause of the disease is related to acute or subacute myocarditis [2].

Asymmetrical hypertrophy was present in all cases of hypertrophic cardiomyopathy in this study. Previous studies of longer duration reported both symmetric and asymmetric hypertrophy [12, 26-28]. Microscopically, all the specimens revealed disarray of hypertrophic myocardial fibers and patchy interstitial fibrosis, reported to be pathognomonic findings in previous studies [27, 29-30].

In cases of tropical EMF, autopsy revealed the typical presentation of the disease described by Davies (1947) and others in previous studies [31-32]. Microscopically, eosinophilic infiltrates were not detected in our autopsies while they have been reported by others [15, 33]. Our findings are in agreement with some previous studies which have stated that eosinophilic infiltrate may not be detected in this disease and suggested that there might be transient earlier bouts of moderate eosinophilia with either spontaneous resolution or progression to low-grade endomyocarditis and gradual progressive fibrosis [33-34].

Eosinophilic infiltrates were detected in cases diagnosed with Loffler's endocarditis. This agrees with the observation that Loffler's endocarditis and tropical EMF represent the same disease process but at different stages [35].

In the present study, arrhythmogenic right ventricular cardiomyopathy was of the fibrolipomatous type. Previous studies, performed over a longer period, identified two main histological patterns: lipomatous transformation or fibrolipomatous transformation of the right ventricular free wall [36-37].

Biventricular involvement was present in one of the 3 cases in our study but in a previous study conducted on 21 cases with arrhythmogenic cardiomyopathy disease, biventricular involvement was observed in 13 cases, isolated involvement of the left ventricle in 4, and isolated involvement of the right ventricle in another 4 cases [36].

5. Conclusion

Cardiomyopathies are an infrequent cause of sudden cardiac death. All deaths occurred in children and adults. They are diagnosed only at autopsy, so they are of high social impact that demands multidisciplinary research and resources. In all cases of SCD, a forensic autopsy should be carried out as it serves as the only reliable source of information for epidemiological and preventive studies of such cases by identifying the affected family and identifying associated risk factors of the disease as well as the factors triggering SCD. On the other hand, since cardiomyopathies are hereditary, their timely diagnosis can prevent future SCD associated deaths in family members.

Thus, it would be desirable that in the near future genetic studies are included in the autopsy protocol. When a case of SCD is identified, the findings, tissue samples, and the availability of material for a possible genetic study for subsequent assessment of the family will have obvious implications for early diagnosis and identification of high-risk individuals among family members. Also, there is a need to evaluate and refer family members to specialized centers where they can be assessed precisely and receive a comprehensive care.

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