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Forensic pathological and genetic landmarks in sudden cardiac death in the young: An update

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ABSTRACT

An episode of sudden death in a young individual is a dramatic event for family members but also a challenge for cardiologists, pediatricians, forensic pathologists and researchers. In the young population, most of sudden deaths are of cardiac origin, in particular due to hereditary cardiac disorders. The autopsy protocol includes a proper macroscopic heart examination and a comprehensive histological analysis. The identification of pathognomonic histopathologic findings may help to unravel the cause of death, but microscopic features are often non-specific and highly ambiguous. Negative autopsy leads to classify the decease as a sudden arrhythmic death syndrome despite concealed cardiomyopathies may be also suspected. The molecular autopsy helps to identify the pathogenic genetic alteration associated with the arrhythmogenic episode leading to the sudden cardiac death. Due to genetic diseases, clinical assessment and genotype-phenotype correlation of relatives is mandatory to early identification of family members at risk and thus adoption of preventive measures, especially in asymptomatic genetic carriers. Specialized teams must carry out a personalized interpretation, integrating all the autopsy findings along with the family history to obtain a conclusive cause of the sudden death. In this review we pretend to update these critical issues.

1. Introduction

Sudden death (SD) is defined as an unexpected decease occurring within first hour of the onset of symptoms or when death occurs unwitnessed within 24 h of the deceased being seen alive and apparently healthy, according to World Health Organization (WHO) [1]. An episode of SD could due to several possible causes, but most of the cases are of cardiac origin and namely sudden cardiac deaths (SCD). More than 4000 years ago, in ancient Egypt, unexpected death was already associated with cardiac cause, as the Ebers papyrus narrates: "*If a patient has pain in*

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the arm and left side of the chest, there is a threat of death". Currently, SCD is a major international public health problem accounting for approximately 15–20 % of all deaths in the Western World. The incidence of SCD is between 50 and 100 per 100,000 population in a range of different countries due to no internationally agreed definition [2,3].

Nowadays, coronary artery disease (CAD) with evolving acute myocardial ischemia is the pathology most frequently observed in SCD in population older 40 years old [4,5]. However, in young population (sudden cardiac death in the young, SCDY), hereditary cardiac disorders (HCD) account for a majority of cases, especially cardiomyopathies [6]. About the 5 % of all the forensic autopsies and the 30–40 % of the autopsies of SCD in the young are non-conclusive, failing to find the cause of the death either because of the absence of the anomalies or because only features of uncertain significance are found [7,8].

Accurate cardiopathological examination is always required in these cases (Fig. 1). In the absence of structural abnormalities ("*mors sine materia*"), despite detailed histopathologic examination and toxicology screen, malignant arrhythmias due to ion channel disturbances should be suspected (called primary electric diseases or cardiac channelopathies), then classified as sudden arrhythmic death syndrome (SADS). In addition, concealed cardiomyopathy should be also taking into account as potential cause of death [9]. It is widely accepted that both clinical as well as forensic diagnosis of these conditions is often challenging, because in the case of the cardiac channelopathies they have not explicit structural stigma, while cardiomyopathies do show macroscopic and microscopic anomalies, but these features can be inconstant/ambiguous and always are non-specific. These controversial situations are usually identified in early stages of the disease, called concealed cardiomyopathies, in which malignant arrhythmias can occur before structural changes occur [10,11].

As said, a proper comprehensive autopsy is imperative to unravel the cause of death. If any suspicious of inherited disease, the subsequent clinical assessment of victim's relatives is an essential step for early identification of relatives at risk and adoption of preventive measures. This group of sudden and unexpected deceases from potentially HCD are usually declined to autopsy. The interpretation of the results of postmortem evaluation of SCD cases is a complex task and uncertainty may exist about the causal relationship between the pathological findings and the unexpected decease. Gross and microscopic examinations were the classic tools of investigation and may identify cardiac abnormalities leading to a definite cardiac diagnosis of cardiomyopathy. Frequently, non-conclusive data is obtained and – as said - nearly 30–40 % of young cases remain then certified as 'unascertained' at postmortem examination [7,8]. In recent years, both high-resolution image (named virtopsy) and massive sequencing genetic techniques have been progressively incorporated to autopsy process, helping to obtain additional data that allows reaching a definitive diagnosis (Tables 1 and 2) [12,13].

In this review we will focus on forensic investigation of unexpected deceases in the young population due to these arrhythmogenic syndromes of genetic origin, mainly cardiac channelopathies (primary electrical diseases or purely arrhythmogenic syndromes) and cardiomyopathies in a way that can allow the forensic pathologist to choose the best operative strategy and then make decisions on whether or not further diagnostic steps are needed.

2. Materials and methods

The research question was to describe the main advances in knowledge about post-mortem diagnosis of the two main causes of sudden cardiac death in the young (channelopathies and cardiomyopathies). Since the broadness of the research question, a non-systematic approach (narrative review) had to be adopted. Pubmed and Google Scholar were used as search engines, using as search terms the main channelopathies ("long QT syndrome", "Brugada syndrome", "catecholaminergic polymorphic ventricular tachycardia") and cardiomyopathies ("hypertrophic cardiomyopathy", "dilatative cardiomyopathy" and "arrhythmogenic cardiomyopathy") associated with the terms "post-mortem", "autopsy", "histopathology" and "molecular autopsy". Three independent reviewers selected the products and compared them, finding full concordance.

3. Hereditary cardiac disorders

During this century, continued technological advances in forensic field have been progressively incorporated in order to help to achieve a conclusive postmortem diagnosis, mainly new electronic microscopy as well as use of high-resolution image methods and massive genetic sequencing [14]. In recent years, these results have been combinate with basic research, mainly molecular/cellular techniques of Human Induced Pluripotent Stem Cells (hiPSC) which have allowed achieve significant breakthroughs in main HCD associated with SCDY: cardiac channelopathies such as long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), as well as cardiomyopathies such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM) [15].

Despite the improvements obtained in the clinical setting as well as in the understanding of cellular/molecular pathophysiological pathways, a significant proportion of families clinically diagnosed with any HCD remain without a conclusive genetic diagnosis, in part due to

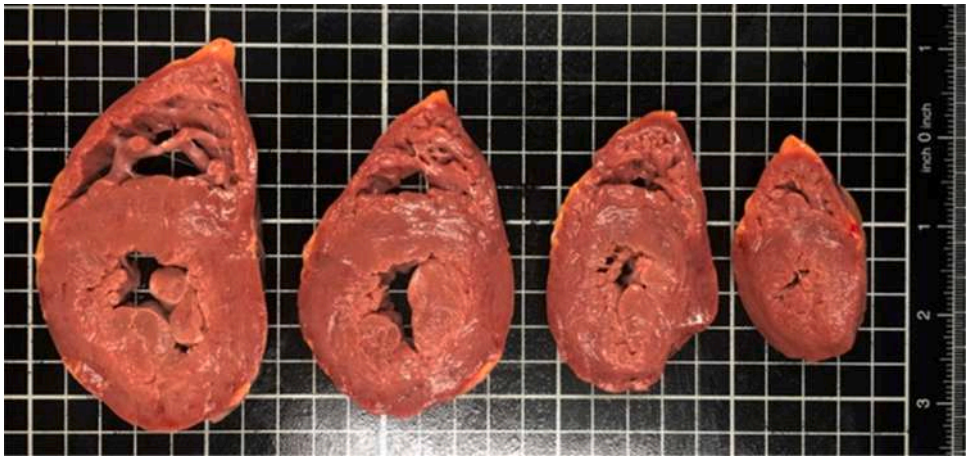

Fig. 1. Gross appearance of dissected heart with advanced concentric hypertrophy of the myocardium (hypertrophic cardiomyopathy). In all the sections, right and ventricular walls are significantly thickened and interventricular septum shows symmetric hypertrophy (thicker than 1,5 cm).

Table 1
Main characteristics in suspected channelopathies. Prenatal, Newborn (0–2 months), Infant (2 months-1 year), Child (1 year-12 years), Adolescent (12 years-18years), Young-adult (18 years-35 years). AD: Autosomic dominant; Brugada syndrome (BrS); Catecholaminergic polymorphic ventricular tachycardia (CPVT); Long QT syndrome (LQTS); SUDY: Sudden Unexpected Death Syndrome.

Autopsy	Main Diseases	Main Genes	Main Inheritance	Main Situation Death	Main Ages SUDY
Suspected Channelopathy	LQTS	*KCNQ1* (40–50 %) *KCNH2* (30–40 %) *SCN5A* (5–10 %)	AD	Exercise Stress Emotion At rest	Prenatal Newborn Infant Child Adolescence
	CPVT	*RyR2* (60–70 %)	AD	Exercise Stress Emotion	Prenatal Newborn Infant Child Adolescence
	BrS	*SCN5A* (15–25 %)	AD	At rest	Prenatal Newborn Infant Young-Adult

Table 2
Main characteristics in diagnosed and suspected cardiomyopathies. Child (1 year-12 years), Adolescent (12 years-18years), Young-adult (18 years-35 years). Arrhythmogenic cardiomyopathy (ACM); AD: Autosomic dominant. Dilated cardiomyopathy (DCM); Hypertrophic cardiomyopathy (HCM); SUDY: Sudden Unexpected Death Syndrome.

Autopsy	Main Diseases	Main Genes	Main Inheritance	Main Situation Death	Main Ages SUDY
Cardiomyopathy or Suspected Cardiomyopathy	HCM	*MYBPC3* (40–45 %) *MYH7* (15–25 %) *TNNI3* (5–10 %) *TNNT2* (5–10 %)	AD	Exercise Stress Emotion	Child Adolescence Young-Adult
	DCM	*TTN* (15–25 %) *LMNA* (5–10 %) *MYH7* (5 %)	AD		
	ACM	*PKP2* (25–40 %) *DSP* (5–15 %) *DSG2* (5–15 %) *DSC2* (5–10 %)	AD		

incomplete penetrance and variable expressivity [16]. Within SUDY (Sudden Unexpected Death in the Young), different age ranges have been established because different situations of malignant arrhythmia have been described depending on age: prenatal, newborn (0–2 months), infant (2 months-1 year), toddler (1–3 years), child (4–12 years), adolescent/teenager (12–18 years), young-adult (18–35 years). Furthermore, differences have also been seen in the triggering of malignant arrhythmia depending on the genetic predisposition to a certain HCD: exercise, stress, emotion or at rest. Regarding sex, no differences has been reported in most part of HCD since the hormonal change component has not yet occurred. Once adolescence arrives, hormonal changes cause differences in affectation to be observed depending on sex in each of the HCD [17,18].

Henceforth, taking into account all data including age, sex, situation of death, macroscopic and histopathological findings, toxicology, previous clinical history (if available), genetic diagnosis and family genotype-phenotype data is crucial to achieve a definite cause of unexpected decease, according to current recommendations of the Society for Cardiovascular Pathology [19].

4. Long QT syndrome

Long QT syndrome (LQTS) is a rare genetically heterogeneous cardiac ion channelopathy characterized by an extended QT interval on the electrocardiogram (ECG) with an increased risk of arrhythmic syncope, seizures and SCD [20]. The risk of life-threatening arrhythmias is influenced by factors such as age, sex, genotype, QT interval, and exposure to triggers [21]. Clinical diagnosis of LQTS relies on a wide-ranging clinical assessment, family history, and genetic testing. LQTS has a prevalence of 1:2000/1:2500 in healthy live births [17]. However, the actual prevalence may be higher because of variable penetrance and expressivity as well as the presence of phenotypically silent genetic carriers. In a recent retrospective study performed in newborns, males exhibited a significantly lower frequency of LQTS [22]. LQTS is a leading cause of SCD in apparently healthy individuals, accounting for more than 50 % of SUDY [23]. LQTS can be due to a pharmacological treatment or electrolyte imbalance. However, most part of cases are of genetic origin. Currently, more than 15 genes have been associated with LQTS despite 3 remain as main genes, responsible together for almost 75 % of clinically diagnosed cases following an autosomal dominant (AD) pattern of inheritance: *KCNQ1* (40–50 %),

KCNH2 (30–40 %), and *SCN5A* (5–10 %). All other genes are considered minority and responsible all they together for less than 5 % of clinically diagnosed cases. Despite this fact, all genes currently associated with LQTS should be analyzed in a clinically diagnosed family or SUDY case, especially if died during physical exercise or swimming, stress, emotion and at rest.

Focusing on histological features in LQTS, there are very few reports on recurrent microscopic changes to date and no definite clinical significance can currently be drawn. In animal models, a relationship between length of QT and extent of cardiac inflammation has been reported [24,25]. Besides cardiac inflammation, many systemic inflammatory diseases have been associated with QT prolongation, as there is a general correlation between duration and extent of inflammation and autonomic nervous system dysfunction [26]. In post-mortem cases, inflammatory features like intracardiac ganglionitis and fibrosis of the cardiac conduction system have been reported [26,27]. In particular, Rizzo et al. analyzed left stellectomy samples of LQTS and CPVT cases, finding (after immunostaining) T-cell-mediated ganglionitis in LQTS and concentrations of CD3 + and CD8 + T cells/mm2 significantly higher than in controls [28].

5. Brugada syndrome

Brugada syndrome (BrS) is a rare HCD characterized by an increased risk of SCD due to life-threatening ventricular arrhythmias in the absence of structural heart disease [29,30]. The diagnostic requires a type 1 ECG, characterized by a coved-type ST segment elevation of $\geq$ 2 mm in the right precordial leads V1–V3, followed by negative T waves. Diagnostic ECG can be observed spontaneously but also can be unmask by fever, vagal stimulation, electrolyte abnormalities and sodium channel blocker. BrS has a prevalence of about 1:2500 [2]. It is responsible for 4 % of all SCD cases and almost 20 % of SCD in individuals with structurally normal hearts [30]. The first arrhythmogenic event usually occurs between the fourth and fifth decades of life at rest/night, and only less than 5 % of patients suffer their first event before 16 years of age. No male prevalence has been reported so far in young patients, being hormonal role the most probable cause despite it is still a matter of debate [31]. BrS is a genetically inherited HCA despite to date, only one gene has been definitively associated with the disease: *SCN5A*. This gene is responsible for 15–25 % of clinically diagnosed families following an autosomal dominant (AD) pattern of inheritance. More than 15 additional minority genes have been proposed as cause of BrS but explaining all together less than 5 % of cases [17]. Due to lack of conclusive association, only the *SCN5A* gene should be analyzed in a clinically diagnosed family of BrS or SUDY case, especially if died at rest/night.

Despite being a channelopathy, signs of acute and chronic inflammation have been reported in BrS, especially localized in specific areas like the right ventricle outflow tract [32]. Inflammation of this latter area has been proved to relate to arrhythmias, thus to have a clinical significance [33]. Another finding recurrently reported in association with BrS was fatty infiltration of the myocardium, but – differently from fibrosis – a significant correlation between the syndrome and this feature has not been proved [34]. The main sign of chronic inflammation is represented by fibrosis, whose clinical significance in BrS is still uncertain, as whether it is a consequence or a cause of arrhythmias is still to be determined. An important (clinical) differential diagnosis is that between BrS and ACM, since the possible overlap at the ECG, and thus even when a BrS pattern has been diagnosed before death post-mortem investigation should carefully evaluate the presence of fibro-fatty replacement and other anomalies typical of ACM rather than BrS [35,36].

6. Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare HCD characterized by polymorphic/bidirectional ventricular tachycardia or ventricular fibrillation leading to high risk of SCD. CPVT is triggered by exercise or emotional stress and 60 % of patients experience syncope before the age of 40, usually in childhood and adolescence. SCD is the first symptom of the disease in 30–50 % of patients [37,38]. CPVT has an incidence of approximately 1 in 10,000 individuals [38]. CPVT is relatively uncommon in infants, but its diagnosis may be delayed due to arrhythmogenic syncope being considered as benign vasovagal events. The diagnosis of CPVT is confirmed by a normal resting ECG, exclusion of structural heart disease, detection of bidirectional or polymorphic ventricular tachycardia in the stress ECG (sometimes with additional supraventricular arrhythmias) and/or detection of a pathogenic variant in a gene definitively associated with the disease. CPVT is a genetic entity, and 60–70 % of clinically diagnosed cases carry a pathogenic alteration in the *RyR2* gene following an autosomal dominant (AD) pattern of inheritance. Additional minority genes have been associated with CPVT, being responsible all they together for less than 5 % of all cases. Despite this fact, all genes currently associated with CPVT should be analyzed in a clinically diagnosed family or SUDY case, especially if died during adrenergic stress. There currently are no known microscopic features reliably relatable to CPVT.

7. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a common (prevalence 1:500) HCD characterized by significant hypertrophy of the left ventricle (LV) wall, with a wall thickness of $\geq$ 15 mm (or z-score $>$ 2 in children), and not explained by other conditions such as hypertension or aortic stenosis [39]. HCM is the second most common cause of cardiomyopathy in the pediatric population, with an incidence of SCD nearly 5 % in the age group of 8–17 years [40]. Classically, the LV hypertrophy is asymmetric either concentric and diffuse in the LV free wall and the septum or localized in regions like the apical-anterolateral free wall and the posterior septum [39]. HCM typically presents with symptoms such as fatigue, dyspnoea, chest pain, palpitations, malignant ventricular arrhythmias, and syncope leading to SCD [39]. Despite this fact, asymptomatic patients are not rare and first symptom can be the SCD. Moreover, at post-mortem examination, it can be distinguished from the athlete's heart because the maximum thickness is higher than 15 mm (especially if the anterior septum is not involved) and the LV's volume is normal or reduced (Fig. 2) [39].

At the microscopic examination, diffuse or patchy areas in which myocardial cells are hypertrophic (nuclei are box-shaped and cytoplasm is strongly eosinophilic) with possible atypical shapes (e.g., they can appear Y-shaped or spiralled) [41]. Hypertrophy is usually associated with disarray and interstitial/replacement fibrosis (with an inverse relationship between disarray and fibrosis) (Fig. 3) [41,42]. In HCM, disarray concerns more than a tenth of the myocardium and tends to affect the interventricular septum (while it may be of no direct pathological significance even in areas next to the septum, like the anterior and posterior wall of the right ventricle) [42,43]. Desmosomes can appear heavily disorganized, with merged megadiscs, intersecting discs and side-to-side disposition [44]. There can also be microvascular anomalies, with medial-intimal hypertrophy of the intramural arterioles, that can appear embedded in fibrosis [41]. Another recurrent vascular anomaly is the myocardial bridging (i.e., an intramyocardial tract of a coronary artery), but this is a very common finding and its significance and relationship with HCM is still highly debated [45]. Finally, other microscopic anomalies can be found, like clefts, diffuse trabeculation, narrow blood-filled myocardial crypts, elongated mitral leaflets, and expanded extracellular space [46,47].

Concerning origin of the disease, genetic testing should be offered to all patients with a suspected or confirmed clinical diagnosis of HCM [18]. To date, several genes have been reported, explaining the genetic origin in almost 80 % of clinically diagnosed families. There are four

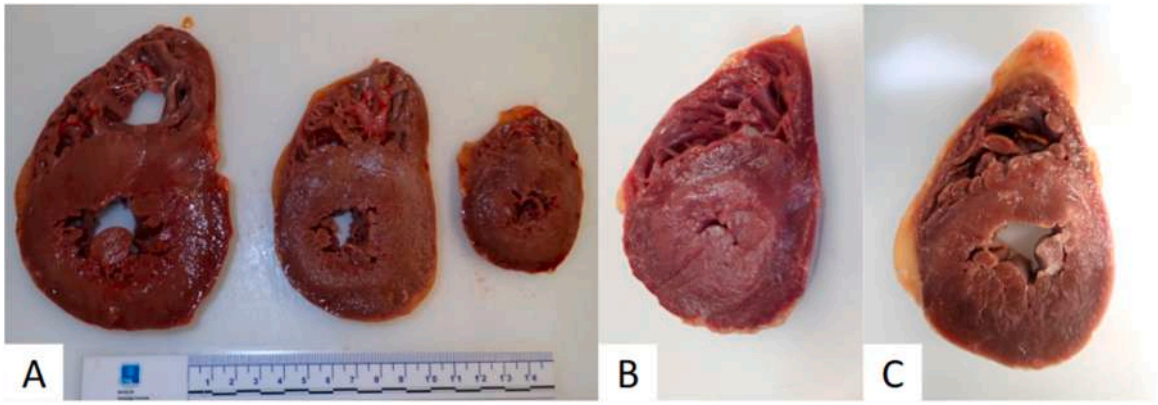

Fig. 2. A - B Macroscopic transversal sections of a heart affected by hypertrophic cardiomyopathy (HCM), characterised by concentric hypertrophy. **C** Macroscopic transversal section of a heart affected by hypertrophic cardiomyopathy (HCM). A post-infarctual scar is visible in the poster-septal wall, involving also the postero-medial papillary muscle.

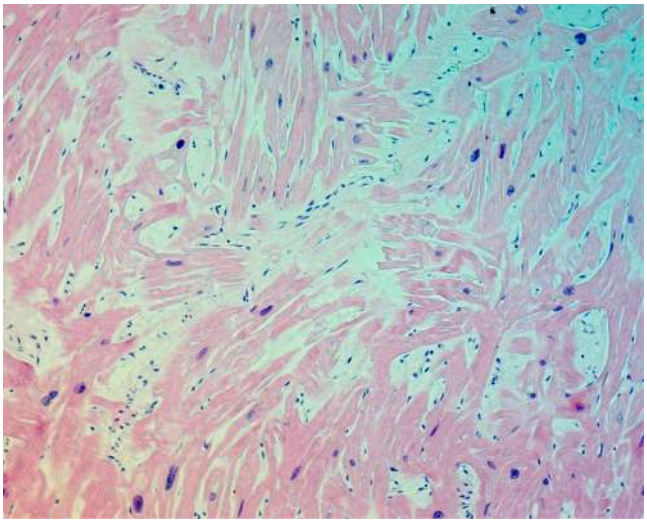

Fig. 3. Right ventricle posterior wall: the myocardial fibers are not aligned as usual. There is a focus of connective tissue with disorganization of the normal parallel architecture (i.d. Myocardial Disarray). Hematoxylin and eosin stain, 10 x magnification.

main genes responsible for the majority of diagnosed cases of HCM; the two most prevalent genes are MYBPC3 and MYH7, which represent 40–45 % and 15–25 % of all cases, respectively. The other two most prevalent genes are TNNI3 and TNNT2, both responsible for 5–10 % of cases (Table 2). All additional genes described so far are considered minority genes, as they are responsible for less than 1–2 % of cases each [17]. The main genes are *MYBPC3* and *MYH7*, accounting for over 40–45 % and 15–25 % of all cases, respectively [17]. Familial HCM habitually exhibits an AD pattern of inheritance [39]. Currently, a genetic testing should include all genes with a definite association with the disease, including minoritary genes. Situation of death usually is during exercise or stress/emotion. It is important taking into account the molecular autopsy showing alterations in any of genes associated with HCM but with no macroscopic even no microscopic findings, suggesting a first stage of an HCM with malignant arrhythmic event before any structural alteration (concealed cardiomyopathies) [11].

8. Dilated cardiomyopathy

DCM has a prevalence of up to 1:250, with up to half of the cases having a genetic/familiar origin, and is the main (55 %) cardiomyopathy in children [48,49]. It is a life-threatening condition, since it can both cause progressive heart failure (representing about the cause of the 70 % of the deaths) and sudden cardiac death (caused by electromechanical dissociation or ventricular arrhythmias) [50]. The diagnosis of DCM is substantially clinical, being based on a dilatation of one or both the ventricles associated to a significant impairment of the LV ejection fraction (Fig. 4) [50]. Some factors like toxins (e.g., cocaine, alcohol, amphetamines, MDMA), drugs (e.g., anthracyclines, lithium, antidepressants, antipsychotics), autoimmune diseases and infectious myocarditis can both cause DCM and catalyse phenotypical progression of inherited DCM [48,49]. One of the main signs of disease is represented by LV remodelling (it is usually thinned, dilated - with a spherical shape, and progressively stiffened – because of the replacement fibrosis) [50].

At the autopsy, DCM diagnosis cannot be only based on LV dilatation, because it is a common finding in highly trained athletes [51]. There is not a direct correlation between the extent of the dilation and the arrhythmic risk, since there are highly arrhythmogenic subtypes that typically show only mild dilation [49]. However, dilatation can cause

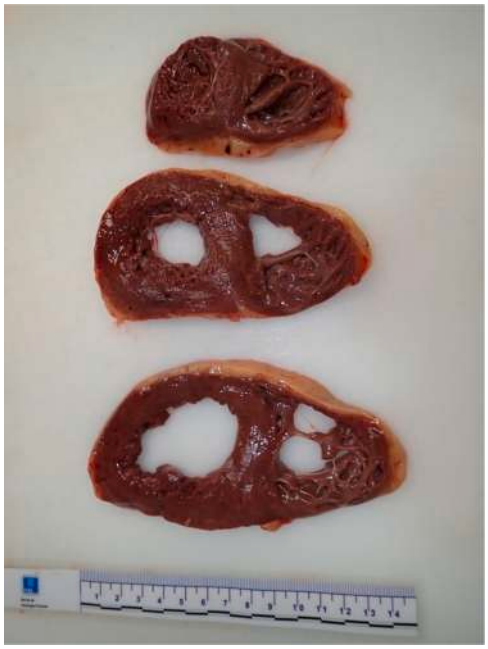

Fig. 4. (DCM) Macroscopic transversal sections of a heart with large and flabby appearance. There is a variable wall ventricular thickness and marcked ventricular dilatation.

macroscopically visible consequences at the autopsy, namely LV mural thrombi (possible foci of embolism) and anomalies of tricuspid and mitral valve (like mitral valve anulus dilatation) [52]. As all the cardiomyopathies, it shows a progressive evolution, with progressive widespread ventricular fibrosis. Fibrosis is an inconsistent feature, caused by inflammation and can be both interstitial and replacement fibrosis [49,50]. It is usually less pronounced than in other cardiomyopathies like ACM and generally more present in the septal mid-wall [49]. Presence of fibrosis in both the septum and the LV free wall is considered a negative prognostic factor because of the higher arrhythmic risk [49]. Besides fibrosis, other common microscopic features are myocyte (eccentric) hypertrophy/atrophy and nuclear pleomorphism (Fig. 5) [51]. Immunohistochemistry can be used to quantify, characterize and localize immune cells and cell-adhesions molecules, while microbiological PCR-based tests can be used to evaluate an infectious cause of the acute/chronic inflammation [50].

The main differential diagnosis is with ischemic cardiomyopathy (DCM is not ischemic by definition), for which a careful coronary arteries dissection must always be considered [49]. DCM must be also differentiated from other causes of LV ventricular dysfunction, like peripartum cardiomyopathy (in which clinical history is essential for differential diagnosis, since the extreme similarities from a macroscopic and microscopic point of view) and left ventricular non-compaction cardiomyopathy (a progressive disease that can cause ventricular dilatation in presence of deep recesses in the free wall and in the apex of LV) [50]. Takotsubo cardiomyopathy should be also considered as alternative diagnosis, and the differential diagnosis is quite complex since they share features like signs of acute and chronic inflammation, but Takotsubo cardiomyopathy is characterized by a specific kind of necrosis (contraction band necrosis) [53].

In near 50 % of DCM cases a familial inheritance is observed and pathogenic variants are usually located main genes: *TTN* (15–25 %), *LMNA* (5–10 %) and *MYH7* (5 %), following an AD pattern of inheritance. Other genes have been also reported in DCM families such as *BAG3, DES, FLNC, PLN, RBM20, SCN5A, TNNC1, TNNT2, DSP, ACTC1, ACTN2, JPH2, NEXN, TNNI3, TPM1* and *VCL* [49]. Currently, diagnostic yield is about 30–40 % [49,54] after a comprehensive analysis of all genes with definite association with DCM. Pathogenic variants of *LMNA* and *FLNC* are considered negative prognostic factors [49]. This fact is important in SUDY cases with no macroscopic/microscopic alterations but carriers of a genetic variant in any of these genes after molecular autopsy.

9. Arrhythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is an entity enclosing arrhythmogenic right ventricular cardiomyopathy (ARVC), but also left (ALVC) and biventricular [55]. It is and HCD characterized by the progressive fibrotic, adipose or fibroadipose replacement of the myocardium, leading to an electromechanical uncoupling of the myocytes and can eventually cause ventricular arrhythmias and SCD during exercise, particularly among young male athletes [55]. Its diagnosis is mainly based on codified clinical criteria (the so-called “Padua criteria”) [56] which consist of major and minor criteria varying according to the three phenotypic variants: classic or right dominant (ARVC), biventricular and left dominant (ALVC). ACM has a prevalence of 1:2000/1:5000 [57].

Main microscopic findings are myocardium atrophy and fibrous/fibrofatty replacement, with fibrosis usually more pronounced than in other cardiomyopathies [49,55]. In this disease, fibrosis’ extent can be

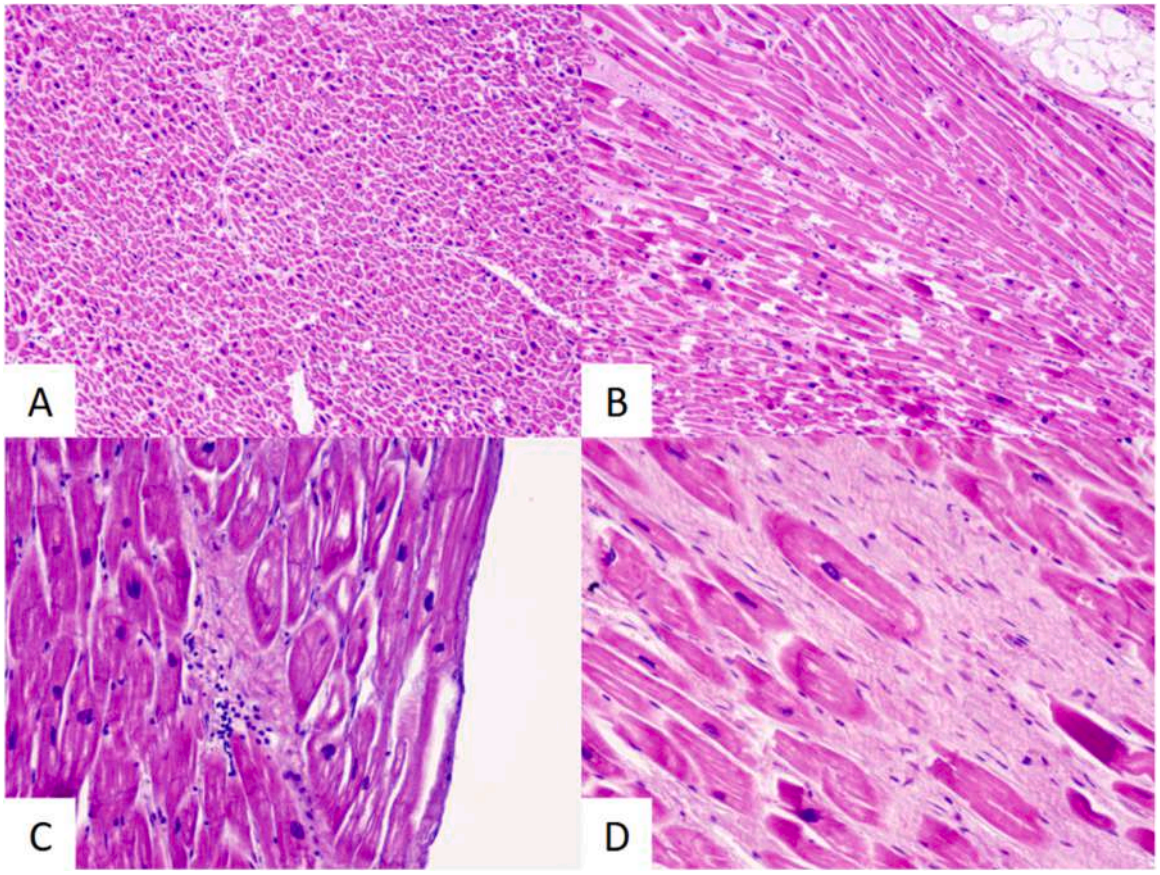

Fig. 5. Hematoxylin and eosin stain DCM: A.B. note the nuclear myocyte variation and the variation in length and diameter of the myocyte nuclei. C.D. replacement fibrosis and foci of inflammatory infiltrate of the left ventricle.

considered as an indicator of LV systolic (dis)function [49]. Signs of disease can be patchy, so multiple samples are mandatory to avoid false negatives [55]. That being said, ventricles – especially the right ventricle - can be affected in the free wall, the outflow/inflow tract and the apex, with the main target represented by the subepicardial inferolateral regions, while the septum may be spared [55]. ACM shows a progressive tendency to transmural involvement following the epicardium-to-endocardium gradient [49,55]. Signs of myocarditis may be present and are generally more pronounced in pediatric/young patients [55]. A common differential diagnosis is with the so-called "*adipositas cordis*", a myocardial fatty infiltration caused by obesity and/or senescence, that can be distinguished by ACM observing the distribution of the fatty cells (following organized patterns, like lingulae) in absence of significant anomalies like fibrosis and loss/atrophy of myocardium [58].

Structural abnormalities of the myocardium are typically studied using contrast-enhancement cardiovascular magnetic resonance (CE-CMR). However, in some cases an endomyocardial biopsy must be performed for the differential diagnosis with disease phenocopies and to exclude mimics, such as sarcoidosis, amyloidosis or myocarditis (Fig. 6) [59].

ACM is a genetic disorder with AD pattern of inheritance, variable expressivity, and incomplete penetrance. It is mainly caused by pathogenic variants in desmosome protein-encoding genes and has a high diagnostic yield (in general 50–60 %, while in pediatric population up to 80 %) [55]. Main involved genes are: *BAG3, DES, DSC2, DSG2, DSP, FLNC, JUP, LDB3, LMNA, NKX2–5, PKP2, PLN, RBM20, SCN5A* and *TMEM43* [55]. Currently, main gens are: *PKP2* (25–40 %), *DSP* (5–15 %), *DSG2* (5–15 %) and *DSC2* (5–10 %). A minority cases of ACM follows an autosomal recessive (AR) pattern of inheritance, as observed in phenotypically characteristic Naxos disease and Carvajal-Huerta syndrome, caused by homozygous pathogenic variants in the *JUP* gene and the *DSP* gene, respectively. In SUDY cases, as occurs in HCM and DCM, first stages of ACM may induce malignant arrhythmias without evident structural alterations, especially if molecular autopsy identifies a deleterious variant in *LMNA, RBM20* and *FLNC* [17,18].

10. Discussion

Since death can be the first phenotypic manifestation of an HCD, post-mortem diagnosis of these conditions is fundamental both for forensic and public health purposes. The forensic value of a correct diagnosis is linked to exclude alternative causes of death that are of legal interest and may show similar or the same features at autopsy, like toxic sudden deaths. On the other side, making post-mortem diagnosis of a congenital cardiac disorder allows for the screening of the first-degree family, in order to promptly detect familiar carriers of pathogenic variants and thus to start early preventive personalized interventions to reduce risk of malignant arrhythmias in relatives.

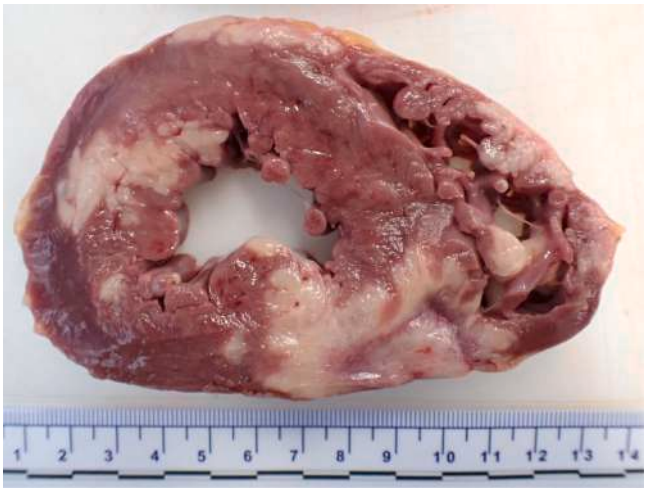

Fig. 6. Macroscopic transversal sections of a heart affected by sarcoidosis widely interested by white scar. There is not an "ischemic" distribution. This finding is nearly pathognomonic for sarcoidosis. Image courtesy of Dr. L. Diaz, Forensic Pathology Service of the IMLCFC.

Among the possible alternative causes of sudden cardiac death, valve defects must be always excluded (Figs. 7 and 8). Valvular heart diseases in native valves cause from 1 % to 5 % of SCD; instead, after valve surgery SCD occurs in 15 %-30 % of the patients [60]. SCD due to mitral valve prolapse is typically arrhythmic and rarely mechanical (caused by cords rupture) [61].

A solid forensic investigations process must always be adopted (Figs. 9 and 10).

Despite cardiomyopathies and channelopathies are considered very distinct entities in clinical practice, early stages of cardiomyopathies can have a very similar microscopic appearance in comparison to channelopathies, sharing the core role played by inflammation. Indeed, signs of acute and chronic inflammation tend to have a prominent clinical significance in both cardiomyopathies (in which the extent and localization of fibrosis, as showed, usually is an important prognostic factor) and channelopathies (in which even acute inflammation is reported to have a direct correlation with arrhythmogenic risk).

To further complicate the diagnostic process, as showed clinical information (on which the diagnosis of many disorders – for instance DCM – is substantially based) are often missing and, when present, can be misleading because of the overlapping clinical presentations, like often in the case of ACM and BrS.

Another central issue is represented by the fact that microscopic anomalies can have patchy/highly variable patterns of distribution in cardiomyopathies (like the fibrous-fatty infiltration in ACM) and especially, when present, in channelopathies (like in BrS, where they tend to localize only inside the outflow tract of the right ventricle). Therefore, we always suggest multiple sampling from different regions of both the ventricles when a congenital cardiac disorder can be suspected at least on familiar basis. Moreover, it is important to collect transmural samples, since many features follow an epicardium-to-endocardium gradient (that is the case of inflammatory infiltrates in BrS and of fibrous-fatty replacement in ACM).

Current genetic technology allows for rapid and low-cost comprehensive genetic analysis, which can include a large number of genes, including the whole exome and genome. However, analysing more genes without a definitive association does not imply greater diagnostic performance in SUDY cases, so only genes with a definitive association with any of the HCD should be analyzed. In these genes, the lack of sufficient basic/clinical data and the restrictive items included in the current classification of genetic variants following the ACMG/AMP guidelines [62] lead to a high percentage of rare variants identified after molecular autopsy remaining classified as ambiguous (VUS). These VUS should not be ruled out until their definitive role in SUDY is clarified. In this way, taking into account all the data obtained during the autopsy, as well as the situation of death, toxicology, previous clinical history and the familial genotype-phenotype correlation can help clarify the potential causal role of a VUS as the origin of SUDY. Current guidelines do not recommend performing familial segregation of a VUS since it is not a clinically actionable genetic alteration; despite this, the guidelines leave open the possibility for each center to implement its own variants of the protocols. Our experience of more than 20 years in the field of SCD suggests that VUS variants should be segregated in family members since, in most cases, a family member diagnosed with any HCD is not a carrier of the VUS, so this variant of ambiguous significance can be eliminated as pathogenic, at least in that family. In consequence, we recommend performing genetic cascade screening in all available relatives, with or without a clinical diagnosis of any HCD as well as symptomatic or asymptomatic, even though clinical measures should not be

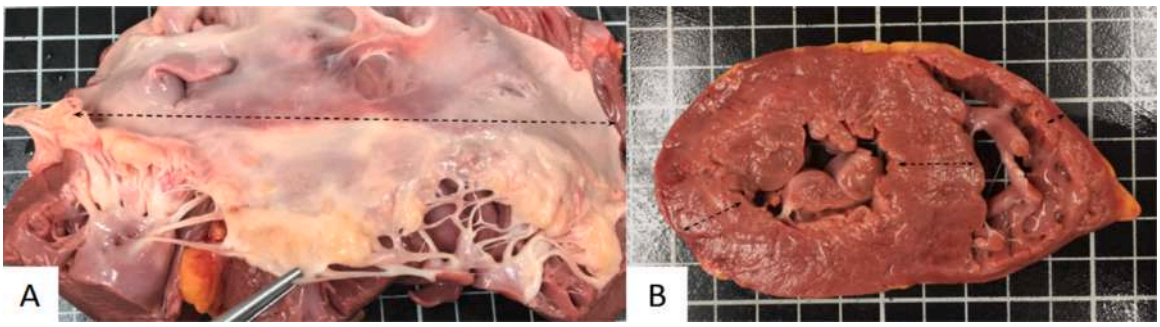

Fig. 7. **A** Macroscopic section of mitral valve (15 cm) of the heart of a 35-year-old man, died of sudden cardiac death at rest. Elongation and fibrosis of both flaps of mitral valve. **B** Macroscopic transversal section of the same heart.

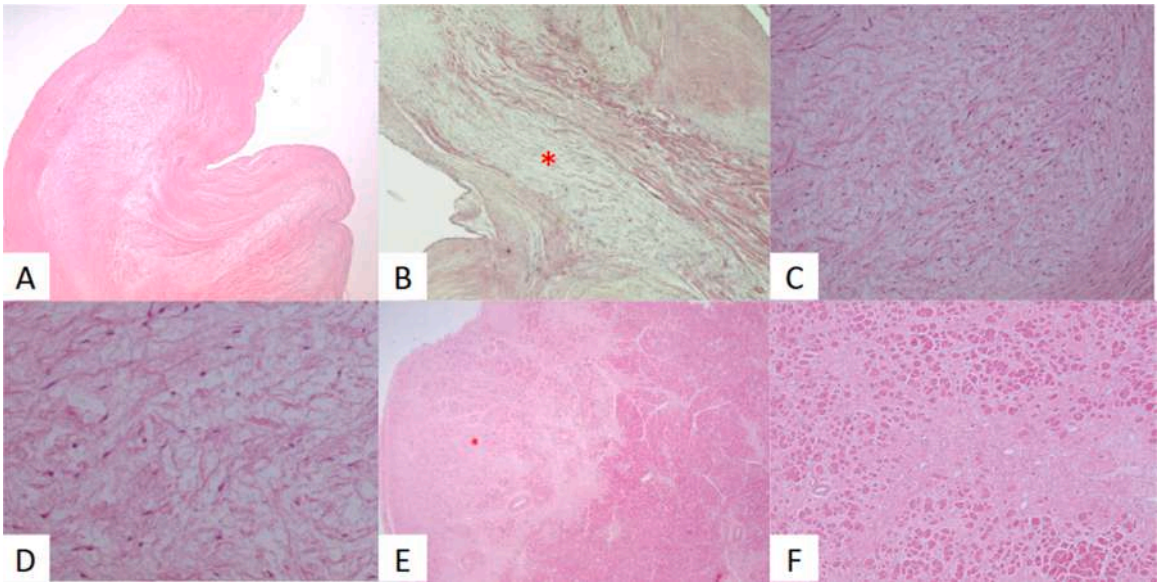

Fig. 8. Histological findings of the same case of Fig. 7. **A B C D** Hematoxylin and eosin stain, different magnification (40 x - 200 x magnification), of mitral valve: fibromyxoid degeneration, increase in collagen fibers and myxoid tissue. **E** Hematoxylin and eosin stain, 20 x magnification, of posteromedial papillary muscle: fibrosis. **F** Hematoxylin and eosin stain, 200 x magnification, of posteromedial papillary muscle: fibrosis.

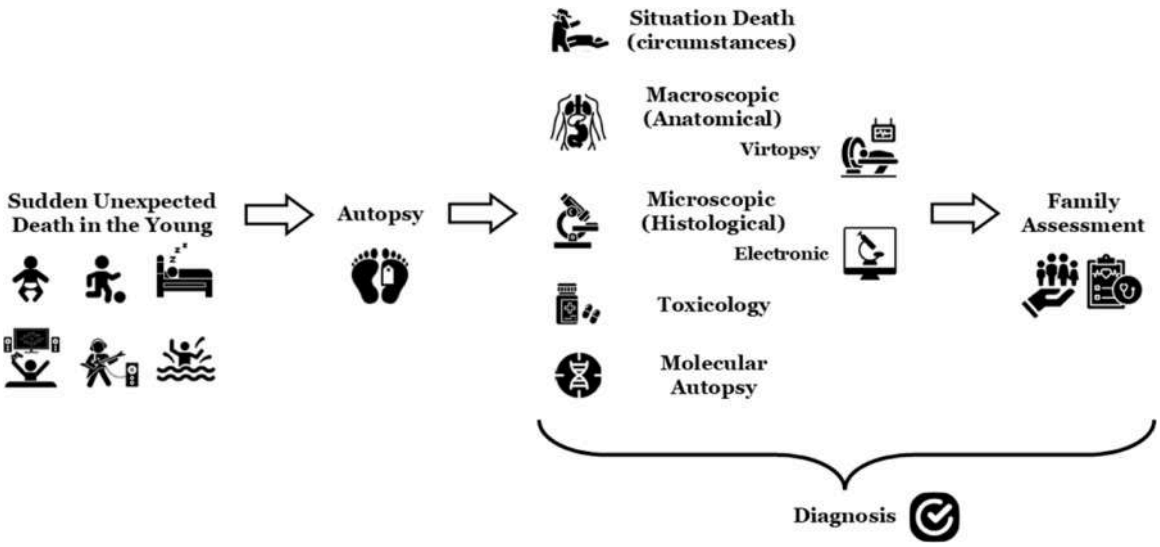

Fig. 9. Overview of the autopsy procedure in SUDY cases. The forensic, clinical and genetic data obtained should be discussed by a multidisciplinary team of experts to reach a definite diagnosis and translate data to family.

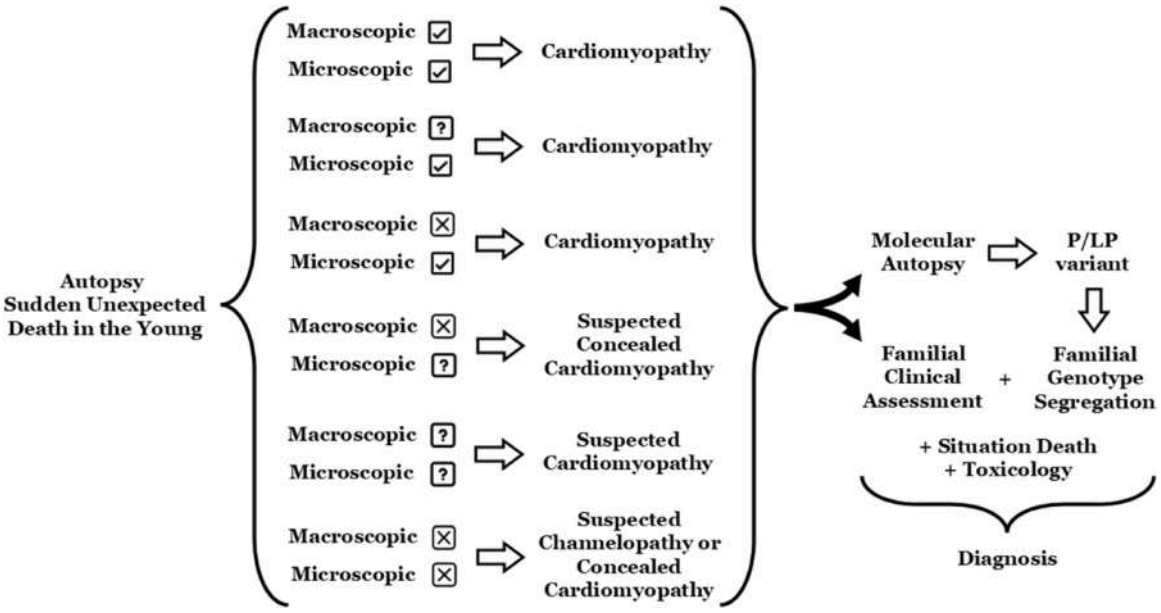

Fig. 10. Overview of the autopsy results in SUDY cases. The macroscopic and microscopic data obtained may unravel the disease or potential disease as cause of death. Taking all data into account help to reach a conclusive diagnosis. LP: Likely Pathogenic; P: Pathogenic.

adopted in genetic carriers of a VUS. Additionally, a periodic reanalysis of VUS should be performed in accordance with ACMG/AMP recommendations to update available clinical/basic studies [8].

Finally, a targeted training is still required because, even if the prevalence of these disorders is relatively high, the opportunity of a post-mortem throughout diagnostic approach is still often missed; so, an accurate macroscopic and microscopic examination is still a challenging step in autopsy procedure.

11. Conclusions

The main cause of an expected decease in the young is hereditary cardiac alterations, which are most often observed in asymptomatic individuals. Nowadays, there are available a wide pool of tools in forensic field helping to unravel a conclusive cause of an unexpected decease. Familial genotype-phenotype are also crucial to interpreted the molecular autopsy but also clinical translation of results. Early identification of genetic carriers at risk is crucial to avoid lethal episodes in relatives. Multidisciplinary teams taking into account all collected data is crucial to reach an explanation of death, but also to treat and advise relatives who may be at risk of suffering a lethal episode.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

All the data that support the findings of this study are in the manuscript.

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