



Molecular Autopsy in Unexplained Sudden Death

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Editorial

Sudden death (SD) is defined as an unexpected natural death in apparently healthy individuals that takes place during the first hour after onset of symptoms [1]. There is a large proportion of SD that remains unresolved, without a definitive diagnosis [2]. This fact is due to medical reports are not accessible in all cases, no autopsy is performed or the cause of death given after autopsy is not specific [3,4].

The autopsy is considered to be negative when all protocol efforts fail to reveal the cause of death [5]. In a typical medical examiner practice, approximately 50% of the deaths are natural, 5–10% unexplained after a gross autopsy, and 1–5% negative after complete autopsy (gross and microscopic examination, and laboratory investigations including toxicological analysis) [6]. Hence, in Europe, recent studies suggest that around 5–10% of the autopsy cases remain unexplained (the so-called “mors sine materia”) [7,8]. This lack of definite cause of death is especially worrying in infant and young-adult population because despite autopsy is performed, no cause of death are identified in most part of cases. In this range of age (<35 years), the death usually happens due to inherited arrhythmias in a structural normal heart [9,10]. Therefore, between 5% and 40% of the so-called autopsy-negative SDs are believed to be due to sudden arrhythmic death syndrome, and genetic testing can be used to confirm the presence of a disease-causing mutation [11]. Despite some significant overlaps, inherited cardiac diseases associated with SCD can be classified into two main groups [12].

Channelopathies, in which the arrhythmogenic substrate is found in the electrical properties of the heart because mutations occurs in genes that encode ion channels proteins. This group includes Long QT Syndrome (LQTS), Brugada Syndrome (BrS), Short QT Syndrome (SQTs), or Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

Cardiomyopathies in which structural abnormalities such as hypertrophy, dilatation or fatty and/or fibrotic infiltration are responsible for inducing the arrhythmia. Research has shown that can be caused by mutations in genes mainly encoding three types of proteins: sarcomeric which cause hypertrophic cardiomyopathy (HCM); cytoskeletal, which cause dilated cardiomyopathy (DCM), and desmosomal, which cause arrhythmogenic cardiomyopathy (AC). All these pathologies are characterized by heart alterations, but in first steps of the disease (usually in young ages of individuals), the structural alteration is not evident during autopsy investigation but arrhythmia may occur, inducing to SD [13].

The post-mortem genetic testing (also named molecular autopsy) has the goal to increase diagnostic yield, facilitating the cascade screening of family members with more focused testing [14,15]. Thus,

it was stated that molecular autopsy should be considered as a part of the comprehensive medico-legal investigation in SCD cases without structural heart alterations [16]. However, post-mortem genetic testing of the proband was reported in only 10% of SCD with no structural alterations patients [17–19], mainly because forensic centres don't have the economic resources to perform genetic testing or don't collect samples due to currently legal restrictions involved with the sampling and storage of DNA [20]. In addition, genetic analysis is usually expensive using traditional methods (Sanger sequencing) but recent development of next generation sequencing (NGS) technologies allow the analysis of an elevated number of genes (even whole exome (WES) or genome (WGS) sequencing) in a reduced time and cost [21]. In a recent study published by our group in young cases died suddenly and without cause of death after complete autopsy, NGS technology identify nearly 35% of cases carrying potential pathogenic variants associated with arrhythmogenic syndromes leading to SCD [22].

Clinical and genetic analysis of relatives is crucial in order to identify family members who may remain undiagnosed and therefore may potentially be at risk of SCD. It has been recommended that all relatives of unexplained SD victims undergo evaluation by a multidisciplinary team of cardiologists, forensic pathologists and geneticists [17,23]. Unfortunately, collaboration between medical genetics departments and cardiology only exists for around 20% of respondents [20]. The link between the post-mortem forensic investigation of a victim and the clinical investigation of surviving family members is difficult to establish. This difficulty may result from legal restrictions. However, legal and ethical issues of post-mortem genetic testing in the forensic context should be considered to inform family members about the potential hereditary risk [24–26]. Finally, we recommend perform a comprehensive molecular autopsy in all forensic cases without cause of death after complete autopsy, especially under 35 years old. If positive, clinical and genetic analysis should be performed in family members in order to early identification of relatives at risk, helping cardiologist to adopt therapeutic measures focused on prevention of new SD episodes.

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