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REVIEW

Sudden cardiac death of arrhythmic origin: Value of post-mortem genetic analysis[☆]



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Abstract Sudden unexplained death refers to sudden deaths that remain without a conclusive cause of death after a complete autopsy has been performed. These cases are classified as deaths of arrhythmic origin, without any alterations in cardiac structure. In recent years, biomedical advances have allowed progressive interaction between genetic research and the forensic field to perform post-mortem genetic analyses, the so-called molecular autopsy. These studies reveal familial genetic alterations that cause heart diseases associated with arrhythmic events and sudden death. Recent post-mortem studies identify genetic alterations as the most probable cause of death in approximately 30% of cases. The results obtained after these analyses also allow for a translation into the clinical field to be made, focused on the early identification of relatives at risk of syncope, as well as the adoption of therapeutic measures for prevention and personalised treatment.

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PALABRAS CLAVE

Muerte súbita inexplicada;

Muerte súbita cardíaca de origen arrítmico: valor del análisis genético *post mortem*

Resumen La muerte súbita inexplicada hace referencia a los fallecimientos repentinos que quedan sin causa concluyente del episodio letal tras realizarse una autopsia completa. Estos casos se catalogan como fallecimientos de origen arrítmico, sin alteración estructural cardíaca.

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Canalopatías;
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En los últimos años, los avances biomédicos han permitido la progresiva interacción entre la investigación genética y el campo forense para realizar análisis genéticos *post mortem*, la llamada autopsia molecular. Estos estudios ponen de manifiesto alteraciones genéticas familiares causantes de patologías cardíacas asociadas a eventos arrítmicos y muerte súbita. Estudios recientes *post mortem* identifican alteraciones genéticas como causa más probable del fallecimiento en alrededor de un 30% de los casos. Los resultados obtenidos tras estos análisis permiten también realizar una traslación al ámbito clínico focalizada en la identificación precoz de familiares a riesgo de síncope, así como la adopción de medidas terapéuticas para la prevención y el tratamiento personalizado.

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Sudden unexplained death

The term sudden death (SD) refers to a sudden and non-violent death which occurs during the first hour from the onset of symptoms or, if it occurs in the absence of witnesses, when the deceased individual has been seen in good physical condition during the 24h prior to the fatal episode.¹ Cases of SD, due to their particular characteristic of being unexpected and sudden, or due to the circumstances that may occur simulating a violent or accidental death or death from poisoning, legally belong to the field of forensic medicine. The medico-legal autopsy of these cases aims to establish the cause of death. In 5–30% of cases, depending on age and the criteria, the autopsy does not identify the conclusive cause of death (blank autopsy).² It has been established that the highest percentages of blank autopsies occur in autopsies performed on deceased individuals from young age groups, while the percentage of SDs without a cause drops considerably in the older population. In these cases, and if an extracardiac cause has been ruled out, the deaths are classified as of cardiac origin, which has been called sudden cardiac death (SCD) of arrhythmic origin in individuals with a structurally normal heart. The term sudden unexplained death (SUD) syndrome was proposed for those cases in which there are no pathological findings in the autopsy, or no pathological or electrocardiographic history before death.³

In most cases, the autopsy identifies the cause of death, with cardiac abnormalities being responsible for almost 85% of SDs. These heart diseases are the leading cause of death in western countries.⁴ An incidence of SCD of 40–100/100,000 individuals/year in the general population, and of 0.46–3.7/100,000 individuals/year in the young population is estimated. This gives an approximate estimation of 1100–9000 annual deaths in Europe and 800–6200 in the USA.^{5,6} In individuals aged over 50 years, coronary artery disease is the main cause of SCD, while cardiomyopathies and channelopathies are responsible for SCD in the younger population.⁷ Cardiomyopathies are characterised as being structural changes to the heart and they are visible during an autopsy, either in the macroscopic or microscopic study. This is due to the fact that they are conditions in which the tissue changes are progressive and to the fact that no

major anatomical changes are visible in the earliest stages of the disease.⁸ Channelopathies are heart diseases which cause malignant arrhythmias associated with SCD, but with no changes to the heart structure. In these cases, the cause of death usually remains unresolved after the autopsy. When there are no indications at all as to the cause of death, it is called a blank autopsy. The death is therefore classified as SUD.⁹ In these cases, the most probable cause of death is suspected to be a cardiac arrhythmia, resulting in the term “*sudden arrhythmic death syndrome*” (SADS).

Cardiac arrhythmias are responsible for around one million syncopal episodes annually, some of them leading to the death of the affected individual.¹⁰ The fatal complications derived from arrhythmias only manifest when there is a perfect interaction between environmental and genetic factors.¹¹ The pathophysiological mechanisms which induce arrhythmias have still not been well defined, although alterations in genes which encode for cardiac proteins have been identified as high-risk factors in the pathogenesis of familial arrhythmias. Epidemiological studies on SUD show that the fatal episode may occur at any age and in both genders equally, despite the fact that there is an established trend that unexpected death occurs either during sleep or during a sporting activity, especially due to coronary artery disease in male adults over 50.^{12,13} Among young adults, SUD is generally related to drug abuse which triggers the cardiac arrhythmia, but more than half of deaths at these ages, especially in children under the age of 15 years, arise from undetermined natural causes.¹⁴ The main inducer in these very young age groups tends to be sporting activity.¹⁵ A heart health check in young athletes is therefore recommended.¹⁶ In infants less than one year old (sudden infant death syndrome [SIDS]), SUD is the main cause of death and tends to occur while they are sleeping.^{17,18} A special group, and one which has been studied in more detail in recent years, is that of patients diagnosed with epilepsy who suffer SUD (sudden unexpected death in epilepsy [SUDEP]). No conclusive cause of death or of traumatic death secondary to an epileptic seizure is discovered in the autopsy.¹⁹ In recent epidemiological studies in this SUDEP group, it has been observed that SUD is the main cause of death in young epileptic patients.²⁰ There may be various mechanisms involved in SUDEP which, in isolation or in conjunction, result in SUD.²¹ Therefore,

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