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Molecular Autopsy in SIDS Cases

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Post-mortem Genetic Analysis in Sudden Infant Death Syndrome

Sudden Infant Death Syndrome (SIDS) is defined as the sudden unexpected death of an infant less than 1 year of age that remains unexplained after a thorough investigation. It includes performance of a complete autopsy, review of the circumstances of death and clinical history. Regarding cause of death, if the autopsy remains inconclusive, inherited arrhythmogenic disorders should be suspected as the main potential cause of decease. Currently, inherited cardiac diseases associated with SCD can be classified into two main groups [1]. 1. Channelopathies; arrhythmogenic substrate is found in the electrical properties of the heart because mutations occurs in genes mainly encoding ion channels or associated proteins. This group includes Long QT Syndrome (LQTS), Brugada Syndrome (BrS), Short QT Syndrome (SQTS), or Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). All these disease are characterized by electrical disruption in structural normal heart [2]. However, recent studies reported mutations in genes encoding structural proteins as cause of arrhythmia in a normal heart [3]. This is a new window of analysis considered improbable so far. 2. Cardiomyopathies; structural abnormalities in heart are responsible for malignant arrhythmias. They can be caused by mutations in genes mainly encoding three types of proteins: sarcomeric, which cause mainly hypertrophic cardiomyopathy (HCM); cytoskeletal, which cause mainly dilated cardiomyopathy (DCM), and desmosomal, which cause mainly arrhythmogenic cardiomyopathy (AC). Despite all these pathologies are characterized by morphologic heart alterations, they are progressive pathologies so in the first steps of the disease (usually in young ages), the structural alteration is not evident but arrhythmia may occurs leading to SCD suggesting that electrical disruption may occurs early that structural alteration [4]. However, this a current matter of argue and more studies

should be performed in order to clarify this point.

Therefore, genetic analysis in SIDS cases should include all SCD-related genes, both arrhythmogenic as well as structural genes. Nowadays, nearly 100 genes have been associated with SCD-diseases being economically not viable perform a comprehensive genetic analysis [5]. However, in the last ten years the development of next generation sequencing (NGS) technology allows a complete genetic analysis in a reduced time and in a cost-effective way [6]. Recent studies claims that there are a large proportion of SIDS cases that remain unresolved, without a definitive diagnosis. This fact is mainly 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 [7]. In these situations, a comprehensive genetic analysis may unravel the cause of death (called molecular autopsy). Hence, it should be considered as a part of the comprehensive medico-legal investigation in SCD cases without structural heart alterations, especially in infants and young people [8]. The genetic study is crucial for identify the cause of death in an infant but also for relatives due to all these arrhythmogenic syndrome are inherited and other family members could be at risk of SCD [9]. Therefore, it has been recommended that all relatives of unexplained SD victims undergo evaluation by a multidisciplinary team of cardiologists, forensic pathologists and geneticists [10,11]. Familial analysis allows early identification of relatives at risk of SCD, helping cardiologist to adopt therapeutic measures focused on prevention of new lethal episodes.

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