G59 Inherited Cardiac Diseases and Molecular Autopsy: Perspectives and Limitations

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After attending this presentation, attendees will understand the importance of postmortem genetic testing, as well its limitations for the diagnosis of sudden cardiac death in young adult or in sudden infant death sysdrom (SIDS) cases.

This presentation will impact the forensic science community by presenting the practical approach to a new diagnostic tool in cases of sudden death in the forensic context.

Cardiac diseases of genetic origin are often the cause of sudden death, especially in young individuals. Postmortem genetic testing, also known as molecular autopsy, is recommended in cases of sudden cardiac death with a negative autopsy. These deaths are currently considered to be due to sudden arrhythmic death syndrome, and are reported in up to 40% of sudden cardiac deaths of young adults. The studies performed on cases of sudden infant death syndrome (SIDS) indicate that approximately 5–10% of SIDS is due to defective cardiac ion channels.

Rhythm disturbances observed in genetically determined cardiac diseases are not always lethal, but can have dramatic consequences if the individual is driving or swimming, for example.

Several cases of sudden death resulting from different genetically determined cardiac pathologies will be presented. In some cases, a morphological substrate, such as arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) or hypertrophic cardiomyopathy (HCM) was observed at autopsy and confirmed by histological examination. In others cases without any pathology observed during standard autopsy procedures, and after a negative toxicological analysis, mutations in the three genes most frequently implicated in inherited arrhythmias SCN5A, KCNQ1, and KCNH2 were found. In the remaining cases even the molecular autopsy was negative.

The first case is a 33-year-old man who died after losing control of his vehicle. ARVD/C was found at autopsy. No traumatic lesions were observed and it was determined to be a natural death. The second case is an 18-year-old man who died after a football match. The only significant finding at autopsy was the ARVD/C. In this case, an electrocardiogram recorded a few weeks before his death showed pathological patterns pathognomic for the ARVD/C. In one SIDS case, the molecular autopsy showed mutations in the KCNH2 gene and in another SIDS case a genetic variant in the SCN5A gene. Both have been described in long QT-cases. In the last presented SIDS case, molecular autopsy was negative but a positional asphyxia was evoked after scene investigation and a cartilaginous meta-hyperplasia of the cardiac conduction system was observed.

The major limitations of the molecular autopsy in forensic practice are the cost of the analyses, the accessibility of a competent laboratory and the legal aspects of postmortem genetic testing. The interpretation

of the results and their transmission to the families can also prove to be problematic. Due to the heritability of genetically determined cardiac disease, the autopsy diagnosis is very important for any living relatives. Collaboration with cardiologists and geneticists allows proposing multidisciplinary consultations to them.

In conclusion, the molecular diagnosis of cardiac arrhythmias represents a very useful and attractive tool in cases of sudden death. However, even if the case is presumed to be related to a hereditary cardiac disease the classical guidelines of autopsy practice should be respected (scene investigation, histological examination, toxicological analyses etc.) to avoid the over interpretation of the results of the molecular autopsy. Moreover, due to the heritability of genetically determined cardiac disease, the potential implications for living relatives must be taken into consideration and genetic counseling should be proposed to the family.

Molecular Autopsy, Sudden Cardiac Death, Channelopathies

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