Review Article

Euromediterranean Biomedical Journal
for young doctors
(formerly: Capsula Eburnea)

SUDDEN UNEXPLAINED JUVENILE DEATH AND THE ROLE OF MEDICOLEGAL INVESTIGATION: UPDATE ON MOLECULAR AUTOPSY

Antonina Argo, Cettina Sortino, Stefania Zerbo, Letizia Averna, Paolo Procaccianti

SUMMARY

In the past few years, contributions of molecular biology assays to the investigation of sudden juvenile death have permitted to clarify some of the pathogenetic aspects of sudden arrhythmic death, opening the way to preventive action on victims' relatives.

We reviewed literature on the genetics of sudden juvenile death, and on molecular biology assays performed on autoptic samples.

Biological investigation permits the detection of genetic mutations underlying the susceptibility to sudden cardiac death of individuals with rare inherited forms of arrhythmia (Long QT Syndrome, Brugada Syndrome, Lev's disease etc.) through the analysis of critical sequences codifying for ion channel subunits (HERG, KvLQT1, MinK, Mirp1, SCN5A, KCNQ1, KCNH2, KCNE1, KCNE2).

The main objective of post-mortem investigation in sudden juvenile death is the detection of treatable monogenic inherited disorders, in order to prevent further deaths among the relatives of the deceased patient.

Introduction

Juvenile Sudden Death (SD) has been attracting increasing attention over the past decades. Heart diseases are the most common cause of an unexpected sudden death in all age groups; in young people the main causes include cardiomyopathy, congenital heart disease, myocarditis, genetic connective tissue disorders, mitral valve prolapse or conduction disease, anomalous coronary arteries (1) and tumors (2).

In recent years, the contribution of molecular biology assays to the investigation of sudden juvenile death has allowed to clarify some of the pathogenetic aspects of arrhythmic syndrome-related deaths, enabling preventive actions on the relatives of the deceased patients (3).

The adoption of standardized survey protocols, not yet sufficiently implemented in forensic practice, could lead to an increased identification of the cause of death, and eventually to the application of the relevant morphological and genetic analysis in family members. For this reason, it is important to encourage the propensity of the scientific and clinical communities to create links between clinicians and forensic and molecular investigators.

Address of the authors

[1] *Department of Biopathology, Biotechnology and Forensic Medicine, University of Palermo, Via del Vespro 129, 90127 Palermo, Italy*

***Send correspondence to**: Dr. Letizia Averna, letiave@libero.it*

***Received**: September 22th, 2012 — **Revised**: October 13th, 2012 — **Accepted**: November 5th, 2012*

Material and method

We reviewed literature on the genetics of sudden juvenile death and on molecular biology assays performed on autoptic samples, in order to define an appropriate methodology.

Results

Sudden death in young people (1-35 years of age) is currently described as a sudden natural death occurring within one hour from the onset of new symptoms (4).

Most of the recent progresses in the autoptic diagnosis of sudden unexpected death in adults originate from molecular biology, especially in cases of sudden death without significant morphological anomalies. Detection of mutations linked with functional cardiac pathologies, such as long-QT syndrome, Brugada syndrome or idiopathic ventricular fibrillation, is now considered the first step in finding the cause for such sudden death.

Molecular investigation is necessary to identify the genetic mutations underlying sudden cardiac death susceptibility in individuals with rare hereditary arrhythmic diseases (such as long QT syndrome, Brugada syndrome, Lev's disease, etc.). Several laboratories have identified mutations in genes that encode cardiac ion channels (for example HERG, KvLQT1, Mink, Mirp1 and SCN5A) that underlie channelopathies (4).

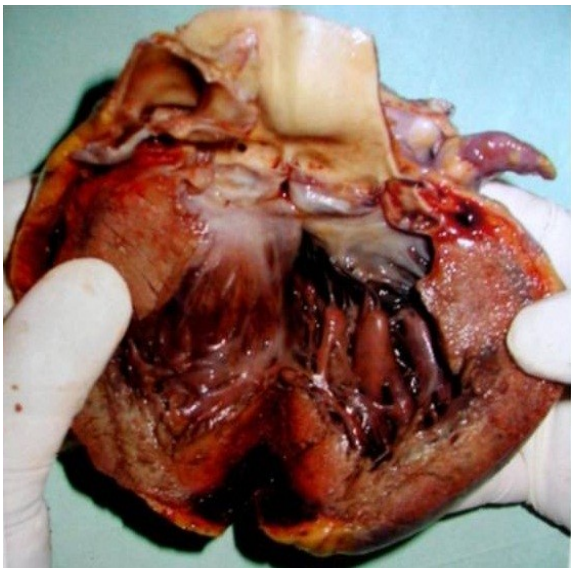

Figure 1: Haemangioma in the apex of the heart

Approximately 50-60% of LQTS is caused by a mutation in one of the several genes that affect the structure or function of ion channels: KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 (5).

Morita and colleagues studied 84 children with idiopathic cardiac hypertrophy diagnosed before 15 years of age, by sequencing the genes MYH7, MYBPC3, TNNT2, TNNI3, TPM1, MYL3, MYL2 and ACTC that encode for sarcomeric proteins that, if mutated, cause adult-onset cardiomyopathies, and the PRKAG2 and LAMP2 genes that code for proteins and metabolites whose mutations cause early-onset ventricular hypertrophy (6).

Hypertrophic cardiomyopathy is the main cause of sudden death in young athletes, and it has been associated with mutations in genes that encode sarcomeric proteins (tropomyosin, troponin T and I, and actin). Recently, new mutations have also been identified in the gene that encodes troponin C (TNNC1: A8V, C84Y, E134D and D145E) (7).

The screening protocol preceding athletic competitions, launched in Italy in 1982 for the prevention of sudden death in young athletes, provided surprising results with the annual incidence of sudden death decreasing by 89%, mainly due to the decline in mortality of athletes with cardiomyopathies (8).

Discussion

Sudden juvenile death is a devastating event for both the family and the community. Over the last decade, significant advances have been made in understanding the clinical and genetic basis of sudden cardiac death in the youth. Many cases of sudden death in young people are related to genetic heart disorders, which can lead to both structural (e.g. hypertrophic cardiomyopathy) and arrhythmogenic (e.g. familial long QT syndrome) abnormalities. Commonly, the sudden cardiac death of a young person can be the first presentation of an underlying heart problem, leaving the family without a reason for why an otherwise healthy young person died (figure 1). Not only is this a tragic event for everyone involved, but it also presents a medical challenge to the clinician(s) involved in the management of the surviving family members. The molecular biology

approach contributes to the etiopathogenetic definition of the early onset of idiopathic cardiac hypertrophy (mutations in MYH7 and MYBPC3), and of cardiac hypertrophy associated with sudden death in young athletes (mutations in the genes codifying for tropomyosin, troponin T and I, actin, and troponin C).
Evaluation of remaining family members requires a multidisciplinary approach that should include cardiologists, a clinical geneticist, a genetic counsellor and a forensic pathologist directly involved in the sudden death case. Therefore, genetic analyses (molecular autopsies) are becoming a useful tool in forensic medicine, allowing the identification and prevention of the causes of sudden cardiac death, as well as improving the chances of an early diagnosis of asymptomatic carriers among relatives.

Conclusion

This article briefly outlines the current understanding of the role of genetics in sudden cardiac death. Furthermore, it also highlights the fact that the molecular biology approach contributes to the etiopathogenetic definition of the early onset of idiopathic cardiac hypertrophy (mutations in MYH7 and MYBPC3), and of cardiac hypertrophy associated with sudden death in young athletes (mutations in the genes codifying for tropomyosin, troponin T and I, actin and troponin C). Performing relevant molecular assays on autoptic samples ("molecular autopsy") is technically feasible and allows the execution of clinical-genetic investigations oriented towards preventative measures among the relatives of the deceased patient.

References

1. Maresi E, Argo A, Spanò G, Novo G, Cabibbi D, Procaccianti P. Images in cardiovascular medicine. Anomalous origin and course of the right coronary artery. Circulation 2006; 22: 609-611.
2. Zerbo S, Argo A, Maresi E, Liotta R, Procaccianti P: Sudden death in adolescence caused by cardiac haemangioma. Journal of forensic and legal medicine 2009; 16: 156-158.
3. Courts C, Madea B: Genetics of the sudden infant death syndrome Forensic Science International; 2010, 203: 25-33
4. Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. Cardiovasc Res 2001;50:399-408
5. Raudenská M, Bittnerová A, Novotný T, *et al*. Mutation analysis of candidate genes SCN1B, KCND3 and ANK2 in patients with clinical diagnosis of long QT syndrome. Physiol Res 2008;57(6):857-862
6. Morita H, Rehm HL, Menesses A, *et al*. Shared genetic causes of cardiac hypertrophy in children and adults N Engl J Med. 2008;358(18):1899-1908
7. Landstrom AP, Parvatiyar MS, Pinto JR, et al. Molecular and functional characterization of novel hypertrophic cardiomyopathy susceptibility mutations in TNNC1-encoded troponin C. J Mol Cell Cardiol. 2008;45 (2):281-288
8. Corrado D, Basso C, Schiavon M, Pelliccia A, Thiene G. Prepartecipation screeening of young competitive athletes for prevention of sudden cardiac death. J Am Coll Cardiol 2008;52(24):1981-1989