

A hypertrophic and dilated cardiomyopathic sudden cardiac death case; de novo mutations in TTN and SGCD genes

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Introduction

Sudden cardiac death (SCD) constitutes one of the most important unsolved challenges in the practice of forensic medicine. Most SCD are caused by hereditary conditions, of which hereditary cardiovascular diseases are the most frequent. More than 20 different pathological entities have been identified as a cause of SCD. Hypertrophic cardiomyopathy (HCM) is the major contributor to overall mortality resulting from ventricular tachyarrhythmia, followed by dilated cardiomyopathy (DCM) (1). The identification of multiple disease-causing gene variants has already improved patient management and increased our understanding of HCM/DCM associated with SCD risk in young adults; however, additional genetic modifiers exist (2).

Herein we report a case of sudden death via DCM/HCM that may be strongly associated with sarcoglycan (SGCD) and titin (TTN) gene variants.

Case Report

A post-mortem examination was carried out to determine cause of death of a 37-year-old man who died suddenly and unexpectedly without pre-existing heart disease. Height of the man was measured as 187 cm and his weight as 90 kg. External examination showed no sign of trauma. Autopsy results are discussed below. Left and right lungs weighed 600 g and 760 g, respectively. Left atrium and ventricle showed chamber dilation. Heart showed abnormalities, including dilated cardiomegaly (cor bovinum, 520g in weight) and giant mitral valve (17 cm in length). No atherosclerotic plaque was found in coronary arteries. No remarkable changes were seen in other organs. Histopathological examinations showed elastic degeneration in spongiotic area, minimal inflammatory elements in mitral valve, nodular fibrosis of chordae tendinae, nucleomegaly, thickening and disorientation of fibers, fibro-hyalinization, and focal mononuclear inflammatory and degenerative cardiomyopathic changes to myocardium (Fig. 1, 2).

Study material for genetic screening of cardiomyopathies was selected from case database at the Department of Forensic Medicine, Near East University (NEU), upon a request from the

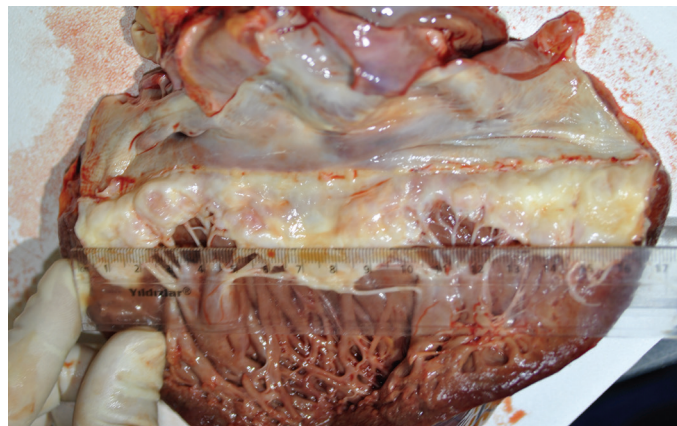


Figure 1. A giant mitral valve (17 cm in length)

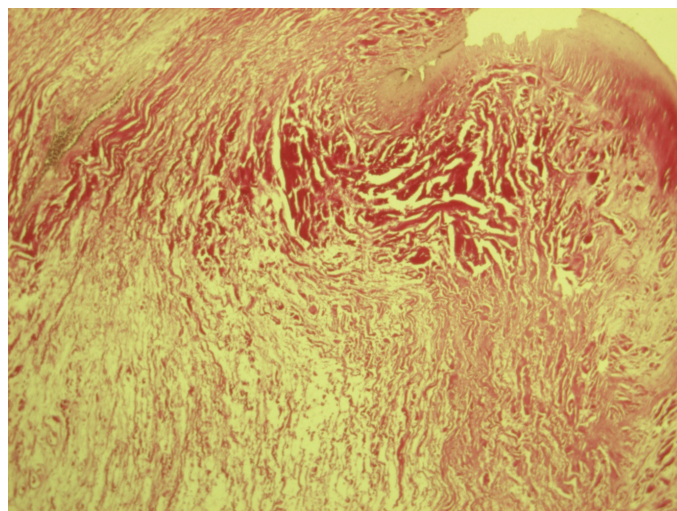


Figure 2. Elastic fibers stained with reddish-pink appearance in hyalinization areas of mitral valve. Elastica-van Gieson stain, x10 objective

local police department. After deoxyribonucleic acid (DNA) isolation process was performed by genetics department, samples were sent to GENetic DIAGnostic Network (GENDIA) for further DNA analyses. Next-generation sequence analysis of coding regions of 40 genes involved in cardiomyopathy and Sanger sequencing confirmation were conducted by GENDIA. Novel missense mutations were identified both in SGCD and TTN genes analyzed. A heterozygous SGCD:c.15G>C a variant with unknown significance (VUS) in exon 3 of SGCD gene, and a heterozygous TTN:c.21758T>C VUS in exon 89 of TTN gene were identified. The cause of death was determined to be sudden circulatory failure resulting from DCM/HCM. Primary genetic counseling was given to his ex-wife and two sons, who were the only family members available at that time.

Discussion

Our findings are TTN and SGCD genes associated with HCM/DCM and DCM, respectively. Different variants within an

individual gene can produce contrasting phenotypes. Each of the cardiomyopathy phenotypes is caused by one of numerous genetic mutations (genetic heterogeneity). Variant interpretation is specifically important with regard to incidental findings that may be inconsistent with the individual's phenotype, and is particularly difficult in autopsy-negative SCD in young people. Genetic analyses of SCD cases that were result of inherited disease show that there are 2 main genetic associations: sarcomere/desmosome proteins, which are associated with cardiomyopathies, and ion channel or regulatory proteins, associated with channelopathies (3, 4). Variant details: NM_000337.5(SGCD):c.15G>C: (p.Glu5Asp) missense variant is present at a population frequency of C=0.0014/167 (ExAC). NM_003319.4(TTN):c.21758T>C (Ile7253Thr) non coding transcript variant or missense variant is present at a population frequency of G=0.0012/148 (ExAC) (5, 6).

Currently, genetic analysis of TTN for diagnosed or suspected cases involving cardiomyopathies should be performed. Despite this fact, only radical variants have been definitively classified as pathogenic (7, 8).

Next-generation DNA sequencing could be crucial to discovery of SCD-associated genes, but large data sets can be difficult to interpret.

Genetic cardiomyopathies merit close study for several reasons. They are frequently early onset and are a major contributor to morbidity and mortality in the young. If a pathogenic mutation can be identified in a family, there is a unique opportunity for diagnosis and intervention at a preventive stage.

Conclusion

Even though autopsy was sufficient to determine cause of death in this particular case, integrating genetic information can give additional insight into the disease and SCD risk.

Comprehensive genotype–phenotype studies in families are necessary to clarify clinical role of these VUS in TTN:c.21758T>C and SGCD:c.15G>C genes.

Acknowledgements: We are kindly thankful NEU Medical Genetics Laboratory and GENDIA Laboratory/Germany for performing the genetic analyses and to Assoc. Prof. Selma Yılmaz Dejgaard for her contribution.

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at www.anatoljcardiol.com
DOI:10.14744/AnatolJCardiol.2016.7270

