"Concealed cardiomyopathy" as a cause of previously unexplained sudden cardiac arrest.

Authors:
J Isbister¹, A Butters¹, J Ingles¹, R W Sy², R Bagnall¹, C Semsarian¹, ¹Centenary Institute, The University of Sydney - Sydney - Australia , ²Royal Prince Alfred Hospital, Cardiology - Sydney - Australia ,

Topic(s):
Gene Variants

Background: Current genetic testing guidelines recommend against broad, multi-phenotype genetic testing in survivors of sudden cardiac arrest (SCA) where no cause is identified on clinical screening. Recent reports describe malignant arrhythmic events preceding detectable structural changes in patients with pathogenic variants in cardiomyopathy genes, who go on to demonstrate structural changes in follow up.

Purpose: We sought to investigate the utility of a broad genetic testing approach, sequencing genes implicated in both arrhythmia syndromes and cardiomyopathy, in SCA survivors where no cause was identified after thorough clinical evaluation.

Methods: We retrospectively reviewed the clinical and genetic profiles of SCA survivors referred to a specialised genetic heart disease multidisciplinary team in Australia. Multi-phenotype genetic testing included analysis of 174 cardiac genes associated with arrhythmia or cardiomyopathy.

Results: The cohort was comprised of 86 SCA survivors. A clinical diagnosis was made in 46 (53%) patients while 40 (47%) cases were considered idiopathic, with no cause of arrest identified despite thorough clinical investigation. Thirty-two survivors of idiopathic SCA (80%) underwent broad, multi-phenotype genetic testing through genome (n=1), exome (n=26) or extended panel (n=5) analysis. The majority of the cohort were male (62.5%, n=25) and ≤35 years of age at time of arrest (60%, n=24). Events in this group most commonly occurred at rest or sleep (65.8%, n=25) and 5 patients had a family history of sudden death (12.5%).

Seven disease causing variants were identified with a testing yield of 21.9%. There was no difference in demographic or clinical factors between those with and without a disease-causing variant.

Six (85.7%) of these clinically actionable variants were identified in genes associated with cardiomyopathy (PKP2, MYBPC3, DES, DSP and ACTN2) that would not have been analysed on a standard commercial cardiac arrhythmia panel. Cardiac magnetic resonance (CMR) imaging was performed prior to genetic testing in 4 of the 6 cases found to have disease-causing variants in cardiomyopathy genes (2 patients did not have CMR performed due to the presence of cardiac devices), with 2 (50%) showing sub-diagnostic changes while 2 (50%) revealed a structurally normal heart.

Conclusion: A broad approach to genetic testing in idiopathic SCA can improve care for patients and their families by identifying clinically actionable variants that would be missed by phenotype specific gene panels and thus significantly increase the rate of diagnosis. "Concealed cardiomyopathy" represents a clinical challenge in how to manage patients and their relatives who carry a pathogenic cardiomyopathy variant, have no overt signs of structural disease, yet have an important risk of sudden cardiac arrest.