P-24

Novel genetic mutation in BAG3 and TNNT2 in a Swedish family with a history of dilated cardiomyopathy and sudden cardiac death

Fernlund E. (1,5), Wålinder Österberg A. (1), Kuchinskaya E. (2), Gustafsson M. (3), Jansson K. (4), Gunnarsson C. (2,6)
Division of Pediatrics, Department of Clinical Experimental Medicine, Linköping University, Linköping (1),
Department of Clinical Genetics, and Department of Clinical Experimental Medicine, Linköping University, Linköping (2),
Department of Cardiology, Department of Medical and Health Sciences, Linköping University, Linköping (3),
Department of Clinical Physiology, Department of Medical and Health Sciences, Linköping University, Linköping (4),
Pediatric Heart Center, Lund University, Lund (5),
Centre for Rare Diseases in South East Region of Sweden, Department of Medical and Health Sciences, Linköping University, Linköping (6),
all Sweden.

Introduction: Familial dilated Cardiomyopathy (FDCM) is a rare cause of Dilated Cardiomyopathy (DCM), especially in childhood. Our aim was to describe the clinical course and the genetic mutations in a family with a history of sudden cardiac death and dilated cardiomyopathy, in which the proband was a four-month old infant presenting with respiratory problems due to DCM. In the family there was a strong family history of DCM.
Methods: DNA was analyzed initially from the deceased girl using next generation sequencing including 50 genes involved in cardiomyopathy. A cascade family screening was performed in the 3-generation family after identification of the TNNT2 and the BAG3 mutation in the proband. Mutation carriers underwent clinical examination including biochemistry panel, cardiac ultrasound, Holter ECG and exercise stress test.
Results: The index patient presented with advanced DCM. After a severe clinical course, the baby had external left ventricular assist as a bridge to heart transplantation. 1.5 months post-transplant the baby suffered sudden cardiac death (SCD) though maximal treatment in the pediatric intensive care unit. The patient was shown to have two heterozygous genetic variants in TNNT2 c.518G>A (p.Arg173Gln) and BAG3 c.785C>T (p.Ala262Val). Three of five screened individuals (two females) appeared to be mutation carriers in the family. The mutation carriers of TNNT2 mutation presented with DCM, two patients had mild or moderate symptoms of heart failure and reported palpitations but no syncope or presyncopal attacks prior to the genetic diagnosis. The mutation carriers of TNNT2 and BAG3 mutation had more advanced DCM. In the second generation of the family there was two additional cases of SCD due to DCM, diagnosed by autopsy, but no genetic analysis was possible in these cases.
Conclusion: Our findings suggest that the mutations in TNNT2 and BAG3 are associated with a high propensity to life-threatening cardiomyopathy presenting from childhood and young adulthood.