Prevention

Outcomes of post mortem genetic diagnosis in SCD victims and primary prevention of cardiac arrest in relatives: a nationwide multidisciplinary and multicentric collaboration in the Czechia

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Introduction: Post mortem genetic analysis in sudden cardiac death (SCD) represents an important diagnostic tool for the primary prevention of cardiac arrest in victim´s relatives.

Purpose: To assess the underlying molecular pathogenesis of SCD in a representative Czech cohort and to evaluate the effects of primary prevention of SCD in genetic relatives.

Patients and Methods: Between 2016 and 2020 we have ascertained 100 SCD cases (29 females/71 males; age range 0-52 years). According to autopsy protocols, cases with SCD were divided into categories of sudden arrhythmic death (SADS), sudden unexplained death (in infants; SUD/SUDI), thoracic aortic aneurysm/dissection and cardiomyopathy hypertrophic, arrhythmic, dilated (HCM, ACM, DCM) and sudden infant death syndrome (SIDS). DNA was isolated from post mortem biopsies / relatives blood and subjected to massively parallel sequencing (Illumina, USA) comprising custom-made candidate gene panel (100 genes). Genetic counselling and cardiological examinations were carried out in 245 family members.

Results: According to post mortem-established diagnosis, we identified 20 victims with SADS and SUD/SUDI, 11 with HCM and DCM, 19 with ACMG, 8 SIDS cases and 9 acute dissection cases. Most of victims died at sleep or at rest, while only 10/100 victims died during strenuous sport activities. About 50% of SCD victims did not report any apparent cardiac complaints. Highly likely or certain molecular etiology (i.e. based on presence of ACMG.net Class 4 to 5 variants) was disclosed in 19/100 (19%) in RYR2, KCNH2, SCN5A, FLNC (stop), TTN, RBM 20, LMNA/C, PRKAG2, MYBPC3, DSC2, FHL1, TGFBR1 and Col3A1 genes (see Tab). Finally, we identified 52/241 phenotype/genotype positive family members who are at risk of cardiac arrest and were offered corresponding cardiological care.

Conclusion: Multidisciplinary cooperation, together with centralized and standardized molecular genetic testing, enables the primary prevention of cardiac arrest in relatives of SCD victims.

Results of post mortem genetic analysis

Post mortem diagnosis	Nr.	Gender	Age (years)	Nr. of positive cases (DNA variant class IV or V)	Gene	Nr. examined relatives/ phenotype or genotype positive cases
SADS	20	8 females 12 males	3-52	5/20 (25%)	KCNH2 3x RYR2 RANGFR	56/11
SUD/SUDI	20	5 females, 15 males	0-50	1/18 (5%, 2 non informative cases)	RYR2	45/9
HCM	11	0 females 11 males	14-52	3/11 (27%)	MYBPC3 FHL1 PRKAG2	26/9

Post mortem diagnosis	Nr.	Gender	Age (years)	Nr. of positive cases (DNA variant class IV or V)	Gene	Nr. examined relatives/ phenotype or genotype positive cases
DCM	11	3 females 8 males	8-48	4/11 (36%)	TTN (3x) RBM 20 FLNC (stop)	24/7
ACM	19	9 females 10 males	17 - 49	4/19 (21%)	SCN5A FLNC (stop) DSC2 LMNA/C	58/9
SIDS	8	3 females 5 males	< 1	0/8	-	12/0
Acute dissection	9	1 female 8 males	16-49	2/9 (22%)	TGFBR1 Col3A1	24/7