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AN INTERPLAY OF GENETICS AND INFLAMMATION AFFECTING LEFT VENTRICULAR REVERSE REMODELLING IN DILATED CARDIOMYOPATHY

Dr. Anna Chaloupka, Ph.D.

Inherited Cardiac Conditions Clinic Lead

CENTRE FOR CARDIOMYOPATHY DIAGNOSTICS AND THERAPY

Ist Department of Internal Medicine Cardio-angiology,

St. Anne's University Hospital and Medical Faculty,

Masaryk University, Brno

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INTRODUCTION - DCM

- defined by the presence of left ventricular (LV) or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment
- causes of DCM can be classified as
  - Genetic - spectrum of genes associated with DCM is broad
  - Non-genetic (inflammatory, connective tissue diseases, endocrinologic, infiltrative, medications and toxins, tachycardia-induced DCM)
- prevalence 1:250, young, most frequent indication for HTx

Elliot et al. EHJ 2008;29:270-276.

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RODCM

- recent-onset dilated cardiomyopathy (RODCM)- diagnosis is made within 6 months
- LV reverse remodelling (LVRR) - decrease in chamber volume and improvement in function; has a positive impact on prognosis. May occur spontaneously or more often in response to therapeutic interventions.
- the course of the disease is unpredictable, from relatively mild to severe and rapid, progressing to death - typically, the prognosis is poor with a 5-year mortality of 46%
- Understanding the underlying aetiology could improve risk stratification of patients with RODCM.

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AIMS & METHODS

- aimed to determine the genetic background of RODCM by whole-exome sequencing (WES), evaluate the inflammation by endomyocardial biopsy (EMB) and correlate these findings with LVRR in the 12-month follow-up
- single-centre prospective observational study enrolled 83 RODCM patients who underwent whole-exome sequencing, EMB and 12-month clinical and echocardiographic follow up.
- LVRR was defined as an absolute increase in LV ejection fraction > +10% and a relative decrease of LV end-diastolic diameter > -10% at 12 months.
- Inflammation was defined according to TIMIC immunohistochemical criteria as the presence of > 7 CD3+ lymphocytes/mm^2 and/or > 14 infiltrating leukocytes (LCA+ cells/mm^2) in EMB samples.

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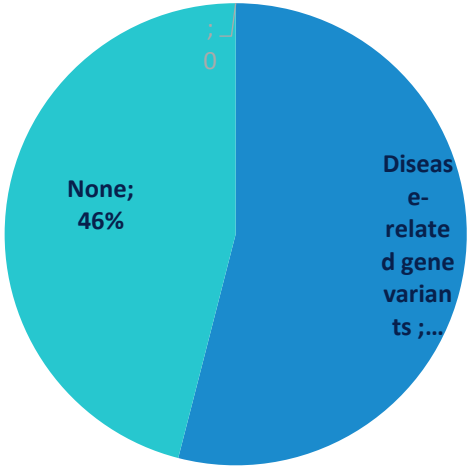
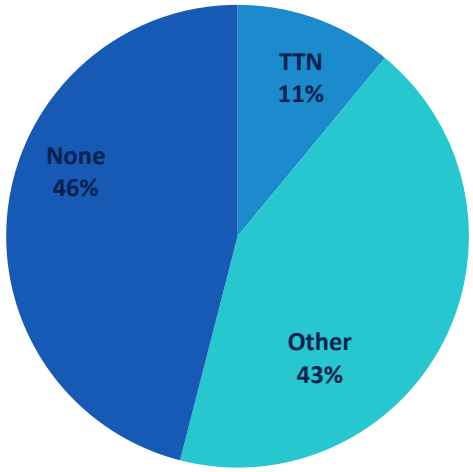
RESULTS



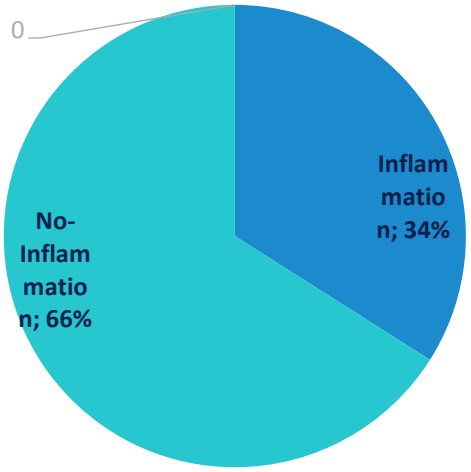
WHOLE EXOME SEQUENCING

WES identified disease-related gene variants (ACMG class 3-5) in 45 (54%) patients.



DETECTED GENE VARIANTS

Majority of the 28 detected genes were represented by variants of titin (TTN) in 9 (11%), other cardiomyopathic genes in 36 (43%) and none in 38 (46%) patients.



ENDOMYOCARDIAL BIOPSY RESULTS

EMB analysis uncovered inflammation in 28 (34%) cases.

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RESULTS

RELATIONSHIP BETWEEN THE RESULTS OF WHOLE-EXOME SEQUENCING, EMB AND LVRR

	No genetic variant N = 38	Titin N = 9	Other genetic variant or more N = 36	P-value
LVRR [N (%)] Δ LVEF > + 10 % and Δ LVEDD < -10%	16 (42%)	5 (56%)	7 (19%)	0.041*
LCA + or CD3 +	15 (39%)	4 (44%)	9 (25%)	0.66
LCA - and CD3 -	23 (61%)	5 (56%)	27 (75%)	

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RESULTS

RELATIONSHIP BETWEEN LVRR AND EMB RESULTS

	LCA + or CD3+	LCA- and CD3-	P-value
LVRR [N (%)] Δ LVEF > + 10 % and Δ LVEDD < -10%	12 (43%)	16 (29%)	0.019*

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SUMMARY OF RESULTS

- LVRR at 12 months occurred in 28 (34%) of all cases
- carriers of non-titin gene variants heralded a lower probability of 12-month LVRR (19%), followed by patients with a negative genetic result (42%) Interestingly, LVRR occurred most often in carriers of isolated TTN variants (56%)
- in contrast, inflammation positively predicted LVRR
- combination of genetic and EMB findings did not predict LVRR in 12 months

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CONCLUSION

- Substantial proportion of RODCM cases has a genetic background and detected myocardial inflammation
- Carriers of non-titin disease-related variants are less likely to reach LVRR, while myocardial inflammation and isolated titin variants predict favourable remodelling in 12 months.
- Further studies – long term follow up regarding reverse remodelling and prognosis (mortality, HTx, ICD therapy etc).

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Thank you for your attention!

Contact:

anna.chaloupka@fnusa.cz

St. Anne's University Hospital in Brno
Pekarska 53, Brno 656 91
Czech Republic

Tel: + 420 543 182 212

www.kardiomyopatie.org

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- Does LVRR mean better outcome?
- Several studies (ELITE, IMPROVE-HF…) have demonstrated that drugs or procedures, which modify ventricular remodeling, are associated with improved outcomes. Reason for HF therapies, including drugs and CRT
- What were the other genes? Titin (TTN) 20–25% of familial DCM; Lamin A/C, Myosin heavy chain, Troponin T, RBM20
- myocarditis may be reversible if the acute inflammatory process heals and the cause viral infection resolves
- Several studies show that TTN variant carriers tend to have milder phenotype and respond better to standard therapy