A tale of twitchy DCM

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Case presentation

• 24 year old male
• Family history of SCD (father)
• Incidental finding of ventricular and supraventricular arrhythmias
• RV and later LV dilatation and moderate systolic dysfunction
• MRI showed no evidence of myocardial fibrosis
• Initial diagnosis of ARVC
Case presentation

Sinus

VES

ventricular bigeminy
Case presentation: Endomyocardial biopsy

Histology showed fibrosis and findings compatible with DCM
Diagnosis?

• Young patient
• High arrhythmic burden with atrial and ventricular arrhythmias, abnormal ventricular activation
• Biventricular dilatation and reduced function
• Family history of atrial arrhythmias, DCM and sudden cardiac death
• Biopsy suggesting DCM with fibrosis and gap junction abnormalities
Genetics of DCM

Genetic analysis for 96 DCM genes revealed a pathogenic SCN5a mutation R222Q

Hershberger et al Nat Rev Cardiol 2013
SCN5a gene function

- SCN5a encodes the α-subunit of the Naᵥ1.5 sodium channel
- Responsible for the fast depolarisation of the myocardium
- Naᵥ1.5 is expressed mainly in the heart (working myocardium and conduction tissue, low expression in SN and AVN)
- Expression gradient from endocardium to epicardium, higher in the endocardium
SCN5a mutations and disease

Extracellular

Intracellular

LQTS/SIDS  Brugada  Rare variant  Rare variant/SIDS

* Previously characterized
Most of the DCM-related mutations are located in the highly conserved homologous S3 and S4 transmembrane segments.
Abnormal cardiac activation

- Abnormal QRS morphology
- Abnormal ventricular activation
- Potential long-term asynchronous electrical activation -> abnormal cardiac load

Royer et al. Circulation 2005
SCN5a and conduction disease

Mouse model of SCN5a+/− heterozygous mice

- Heterozygous
- Wild type

Royer et al. Circulation 2005
Remodelling of gap junction

Downregulation of Connexin 40 and upregulation of N-cadherin in the myocardium

Royer et al. Circulation 2005
SCN5a mutations lead to myocardial fibrosis

Mouse model of SCN5a\(^{+/-}\) heterozygous mice

Picrosirius red

Haematoxylin-eosin

Ventricular fibrosis

Perivascular fibrosis

Royer et al. Circulation 2005
Hypertrophic and stress signalling activation

Abnormal β-MHC and skeletal α-actin in aging heart

Atf3 and Egr1 activation indicating increased cardiomyocyte stress

Royer et al. Circulation 2005
SCN5a-DCM: Clinical characteristics

- Early onset
- Conduction disturbances, unrelated to degree of LV dysfunction
  - Bundle branch block is common
  - Occasionally first degree AV-block
- Supraventricular arrhythmias
  - Atrial ectopic beats (numerous ectopic foci in the conduction system)
  - Atrial fibrillation
- Ventricular arrhythmias
  - Bigeminy, multifocal ectopic beats (Purkinje fibers)
  - Sudden cardiac death
- DCM-phenotype
  - Age-related disease penetrance
- No clear LQT or Brugada signs
Thank you