Arrhythmogenic Cardiomyopathy cases

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Καρδιολόγος
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Α Καρδιολογική κλινική ΑΧΕΠΑ
Definition

ARVD (Arrhythmogenic Right Ventricular Dysplasia)

Progressive loss of RV myocardium and its replacement with fibrofatty tissue
Marcus F et al, Circulation 1982

ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy)

This disease falls within the spectrum of the nonischemic cardiomyopathies classified by the World Health Organization in 1994
McKenna et al, Br Heart J 1994

ACM (Arrhythmogenic Cardiomyopathy)

the more recent recognition of left-dominant and biventricular forms has led to adoption of the broader term
Sen Chowdhry et al, Ann Rev Med 2010
• 1/1000- 1/ 5000
• Second to fifth decade of life
• Uncommon to first develop sighs and symptoms of ACM after the age of 70 yo
Pathology

- **Myocyte degeneration and fibrosis, with or without fat** (the most important histopathological indicator of the disease)
- Myocardial atrophy is a genetically determined process that occurs progressively with time (periodic acute bursts-hot phases)
- Starts from the epicardium and extends to the endocardium to become transmural
- Progressive wall thinning (aneurysms) predominantly at the triangle of dysplasia
Inheritance

- Autosomal dominant pattern
- Incomplete penetrance
- Penetrance is definition dependent
- Variable expression
- Marked intrafamilial phenotype diversity
Desmosome

Cristina Basso, Lancet 2009
Asimaki A Canadian Journal of Cardiology 2015
Non desmosomal gene mutations

- **Ryanodin receptor (Ca release from SR)**
  Juvenile SD and effort-induced polymorphic VT

- **Transmembrane protein 43 (Canada)**
  Inner nuclear membrane
  Premature SD and severe HF

- **Phospholamban**
  First found in DCM

- **Transforming Growth factor 3β (TGF3β)**
  Play a role in cardiac inflammation and fibrosis
• The desmosomes are remodelled and there is abnormalities to cell to cell adhesion

• But is pathogenesis related only to these abnormalities?
• Depressed plakoglobin (γ catenin) to cell to cell junctions

• Cellular redistribution of plakoglobin to the intracellular and nuclear pools → Hallmark for ACM

• β catenin → structural protein and signalling molecule can not replace γ catenin at desmosomes

• Redistribution of plakoglobin may interfere with activity of β catenine
Phenotypic expression is a prerequisite for malignant arrhythmic events and sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy

Our findings also suggest that the ‘concealed phase’ of the disease may be the result of the low sensitivity of routine clinical tests (i.e. electrocardiogram and echocardiography) for detection of early/minor disease phenotypic manifestations such as isolated epicardial scar involvement of the left ventricle, rather than the expression of a subcellular arrhythmogenic mechanism.

Zorzi A et al 2016
1st case

- Female 60 yo
- Right Heart Failure work up
- Anemia
- ESR 100 mm
Background

26/10/2008
Sick sinus syndrome (holter 4,6 sec/ syncope)→ PCM

4/8/2010
VT LBBB (hemodynamic instability-syncope)→ electric sock
CA → 80% LCx → PCI

19/4/2012
• RHF hospitalization (1st diagnosis)
• right pleural fluid
• Diagnosis of pulmonary embolism ? (lung scintigraphy)

3/3/2017
• AHEPA cardiomyopathy lab
• Lopresor 100mg (50 mg bid)
• Lasix 40mg (od)
• Aldactone 25 mg (od)
• Sintrom
Holter

- 3 NSVT episodes
- PVCs = 2067/24 ωρο
• Immune blood test normal
• Gastroscopy- Colonoscopy → normal
• Right heart catheterization and Myocardial Biopsy
ventriculography
Proband

4 major criteria

- (-) T waves V1, V2, V3 (repolarization abnormalities)
- VT – LBBB (superior axis) (arrhythmias)
- RV aneurysm (ECHO and ventriculography)
  RVOT PLAX 4,5 cm
- Residual myocytes <60% (tissue)

- Definite diagnosis
Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia
An International Task Force Consensus Statement

Flow chart for ICD implantation

- High risk
  - Aborted SCD due to FV
  - Sustained VT
  - Severe dysfunction of RV, LV, or both
  - ICD indicated (Class I)

- Intermediate risk
  - ≥1 major risk factors*:
    - Syncope
    - NSVT
    - Moderate dysfunction of RV, LV or both
  - ICD should be considered (Class IIa)

- Low risk
  - No risk factors
  - Healthy gene carriers
  - ICD non indicated (Class III)

Corrado et all, Circulation. 2015
One month later

- Breast Ca
2nd case

- Boy 15 yo
- 24 hours fever
- Angina (-)
- NYHA I
- Syncope (-)
- Palpitations (-)
- Kickboxing (5 months)
Holter
• proBNP 322 pg/ml
• Troponine 7 pg/ml
• Immunological tests (-)

• Carvedilol  6,25 mg 1x2
• Ramipril  5 mg 1/2x1
• Eplerenone  25 mg 1/2x1
Proband

**major criteria**

- Residual myocytes <60% with fibrous replacement of the RV free wall myocardium in 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy (tissue characterization)

**minor criteria**

- NSVT (arrhythmias)
- Negative T waves (V4, V5, V6) (repolarization abnormalities)

1 major + 2 minor      definite diagnosis
• ICD  (30/5/2017)
• ATP  therapy due to VT episode (4/10/2017)
Father
Normal ECG
Normal ECHO
No PVCs
Mother

NSVT holter
Normal ECHO
No ECG criteria
Diagnosis of familial ARVC
(in a context of proven ARVC/D in a first-degree relative)

• T-wave inversion in right precordial leads V1, V2, and V3 in individuals over the age of 14 years

• Late potentials by signal-averaged ECG (SAECG)

• Ventricular tachycardia of left bundle-branch block morphology on ECG, Holter monitor, or during exercise testing, or 200 premature ventricular contractions in 24 hours

• Either mild global dilatation or reduction in RV ejection fraction with normal LV or mild segmental dilatation of the RV, or regional RV hypokinesis
Mother

• 1 criteria

NSVT   Holter

Definite diagnosis
LDAC ACM versus late stage ACM with LV involvement

**LDAC phenotype**
- Ventricular arrhythmia of RBBB morphology
- Additional LBBB phenotype
- Septal LGE
- Negative T waves in inferolateral leads

**Late stage ACM**
- Ventricular arrhythmia of LBBB morphology
- Multifocal arrhythmia less frequently
- The septum is generally spared
- Negative T waves in right precordial leads
LDAC ACM versus DCM

• Midwall enhancement is observed in both, but subepicardial distribution raises suspicion of ACM
• Predisposition to ventricular arrhythmia that exceeds the degree of morphological abnormality and systolic impairment
• Myocyte loss with fibrofatty replacement on histology

Chowdhry SS, et al JACC 2008
Desmoplakin Missense and non-Missense Mutations in Arrhythmogenic Right Ventricular Cardiomyopathy: Genotype-Phenotype Correlation

- 2-12% desmoplakin mutation (ACM cases)
- More often associated with a predominant LV phenotype or biventricular involvement
- Desmoplakin mutations correlates with a high arrhythmic risk
- Non-missense mutations are specifically associated with left dominant forms

Castelletti S et al, Int J Cardiol 2017
Take home messages

- Arrhythmogenic Cardiomyopathy
  - ‘Classic’ ACM
  - Left dominant ACM
  - Biventricular ACM
- Diagnosing criteria are focusing on RV predominance
- Look at the ECGs
- Look at the families
• Many Thanks