ΑΡΡΥΘΜΙΟΛΟΓΙΚΑ ΠΕΡΙΣΤΑΤΙΚΑ με ΜΥΟΚΑΡΔΙΟΠΑΘΕΙΕΣ

Ασθενής με ανεξήγητη βραδυκαρδία

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Cardiomyopathy Clinic

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Unit of Inherited Cardiovascular Diseases
14y male, asymptomatic bradycardia

CLINICAL HISTORY
1st cardiological examination, 2 months ago
(incidental finding: low heart rate)

ECG:
SR, HR~45bpm, otherwise normal

ECHO:
“borderline” normal LV size (EDD=57mm), otherwise normal.

HOLTER:
SR, HRmax:153bpm  HRmin:28bpm, pauses 2,8 sec (10:11) and 2,7 sec (13:50)

MRI:
unable to undergo (claustrophobic)

Re-evaluation in 3 months...
PATIENT EVALUATION in outpatient clinic

Still asymptomatic in “regular” activity (PC addicted...)
Clinical examination unremarkable
Blood tests normal (including thyroids)
Family history: maternal mother died suddenly 40yo, despite PM

SINUS BRADYCARDIA
**ECG:**
SR, HR= 45bpm, otherwise normal

**HOLTER:**
2 pauses

Sinus pause $\approx$ 4.5 sec

Sinus pause $\approx$ 3 sec
LV-EDD = 60mm
dilated, 126% predicted – Henry’s formula
EF~45%
mild segmental systolic impairment

H: 1.63m
W: 72kg.

BSA 1.78m²
WHAT IS THE DIAGNOSIS, so far:

1. Left-dominant arrhythmogenic cardiomyopathy
2. Dilated cardiomyopathy and pro/conduction disturbances
3. Dilated cardiomyopathy and LQTs
4. None of the above
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CARDIOPULMONARY STRESS TEST

<table>
<thead>
<tr>
<th>Peak Cardiovascular Responses</th>
<th>Predicted</th>
<th>Measured</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 (ml/kg/min)</td>
<td>45.9</td>
<td>29.9</td>
<td>65</td>
</tr>
<tr>
<td>VO2 (l/min)</td>
<td>3.120</td>
<td>2.031</td>
<td>65</td>
</tr>
<tr>
<td>VCO2 (l/min)</td>
<td>1.716</td>
<td>2.272</td>
<td>132</td>
</tr>
<tr>
<td>Work (Watts)</td>
<td>168</td>
<td>145</td>
<td>86</td>
</tr>
<tr>
<td>Anaerobic Threshold (AT)(l/min)</td>
<td>&gt; 1.248</td>
<td>1.084</td>
<td></td>
</tr>
<tr>
<td>AT (% Predicted Max VO2)</td>
<td>&gt; 40%</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>207</td>
<td>153</td>
<td>74</td>
</tr>
<tr>
<td>O2 Pulse (ml/beat)</td>
<td>15.1</td>
<td>12.8</td>
<td></td>
</tr>
</tbody>
</table>

Abnormal chronotropic response....

3 days later...

palpitations!...

HOLTER

NSVT ...
Questions to the audience  (2)

The clues...

- Young male with mild LV impairment, unexplained sinus bradycardia, SN dysfunction, NSVT
- Mother with sinus bradycardia
- Grand-mother with SCD despite pacemaker

WHAT IS THE VERY NEXT STEP:

1. Detailed family history and genetic testing
2. Cardiac MRI
3. Coronary angiogram
4. Pacemaker implantation
Questions to the audience (2)

**The clues...**

- Young male with mild LV impairment, unexplained sinus bradycardia, SN dysfunction, NSVT
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**WHAT IS THE VERY NEXT STEP:**

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FAMILY TREE completed...
GENETIC TESTING

Lamin A/C mutation : Q312X
Questions to the audience (3)

WHAT IS THE NEXT STEP:

1. Pacemaker implantation
2. ICD implantation
3. ICD implantation + aMEA
4. Genetic testing to all 1st degree relatives
5. None of the above
6. (3) + (4)
Questions to the audience (3)

WHAT IS THE NEXT STEP:

1. Pacemaker implantation
2. ICD implantation
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4. Genetic testing to all 1st degree relatives
5. None of the above
6. (3) + (4)
For the family...
The **LMNA** gene encodes nuclear lamin A and C, intermediate filament proteins that are components of the nuclear lamina.

**Box 1. Clinical entities caused by LMNA mutations**

- Autosomal Emery-Dreifuss muscular dystrophy
- Cardiomyopathy dilated 1A
- Limb-girdle muscular dystrophy type 1B
- Congenital muscular dystrophy

**Diseases of striated muscle (see also Fig. 1)**
- Emery-Dreifuss muscular dystrophy
- Limb-girdle muscular dystrophy 1B

**Lipodystrophy syndromes**
- Dunnigan-type familial partial lipodystrophy
- Lipoatrophy with diabetes and other features of insulin resistance
- Insulin resistance without lipoatrophy
- Mandibuloacral dysplasia

**Peripheral neuropathy**
- Charcot-Marie-Tooth disorder type 2B1

**Accelerated aging disorders (progerias)**
- Hutchinson-Gilford progeria syndrome
- Atypical Werner syndrome
- Restrictive dermopathy
- Variant progeroid disorders
- Mandibuloacral dysplasia

*Lu. LMNA. Disease Models and Mechanisms 2011*
Patients with LMNA may present a wide range of arrhythmic disturbances, either bradyarrhythmias (conduction disturbances and AV-blocks, sinus node dysfunction, atrial standstill) or tachyarrhythmias (AF, VT, VF), in variable combinations, and with frequent association with LV dysfunction and HF.

Presence of LMNA mutations refers in:
- ≈ 30% of DCM patients with conduction defects
- ≈ 5-8% of DCM pts

Am Heart J; 2007;154:1130-9

Emery Dreifuss muscular dystrophy: wasting of humeral muscle + elbow contracture
AVB, later DCM
Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

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The 4 independent risk factors were nonsustained VT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing). These findings could have important implications for counseling and treatment of affected families carrying LMNA mutations.

Prophylaxis also suggests that ICDs are potentially lifesaving in LMNA mutation carriers. Thus, it seems prudent to consider an ICD in persons with 2 or more of the 4 risk factors identified. Although, further research needs to be conducted to clarify this assumption. Conversely, the low incidence of MVA in the absence of the clinical risk factors nonsustained VT and LVEF <45% suggests that persons carrying a LMNA mutation with a normal ventricular function and no evidence for ventricular arrhythmias can be reassured, but due to the possibility of progression of the disease, it means these persons with such mutations require regular and detailed reassessment for markers of arrhythmic risk (5,10).
**DIAGNOSIS**

**STATE OF GENETIC TESTING FOR DILATED CARDIOMYOPATHY (DCM)**

**Class I (is recommended)**

Comprehensive or targeted (LMNA and SCN5A) DCM genetic testing **is recommended** for patients with DCM and significant cardiac conduction disease (i.e., first-, second-, or third-degree heart block) and/or a family history of premature unexpected sudden death.

Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.

**Class Ila (can be useful)**

Genetic testing **can be useful** for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.

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**MANAGEMENT**

An ICD is recommended in patients with DCM, symptomatic HF (NYHA class II–III) and an ejection fraction ≤35% despite ≥3 months of treatment with optimal pharmacological therapy who are expected to survive for >1 year with good functional status.

A cann device should be considered in patients with DCM and a confirmed disease-causing LMNA mutation and clinical risk factors.
When should we suspect a laminopathy?

- DCM and atrioventricular block or sinus node dysfunction
- DCM and skeletal muscle abnormality
- DCM onset is preceded by supraventricular or ventricular arrhythmias
- Family history of SCD (especially in relatives with a pacemaker implantation)

Only a high index of suspicion and referral for genetic testing are essential to improve the early diagnosis and consequently the prognosis of the affected patients.
Ευχαριστώ για την προσοχή σας...