A case of HCM with left bundle branch block and severe heart failure
No conflict of interest to declare
P.B. ♂ 70 yrs old

Negative family history

Essential systemic hypertension during the last 20 years (treated with ARBs and tiazides)

Partial prostatectomy at 54 yrs
Surgery for carpal tunnel syndrome at 56 yrs
Partial thyroidectomy at 65 yrs

67 yrs: paroxysmal atrial fibrillation (→ aspirin and Atenolol 50 mg/die)

During the last year: progressive dyspnea (NYHA III-IV)

Referred with diagnosis of CHF secondary to HHD
P.B. ♂ 70 yrs old

Physical examination:
• SR at presentation
• BP = 120/95 mmHg
• Bilateral lung crepitations
• Third heart sound
• Mild bilateral legs edema

Routine lab tests:
• Serum creatinine 1.6 ml/min (GFR = 45 ml/min)
• Microalbuminuria
ECG (during a phase of atrial fibrillation)
P.L., 70 yrs

Relevant ECHO measurements

IVS 21 mm, PWT 19 mm
LV EDD 45 mm; LV ED-Vol 92 ml (45/m²)
LV EF 60%
Asc. Ao 3.2 cm ; LA 4.2 cm
E wave DT 115 msec E/A 2.5
S wave 5 cm/sec
E/E’ = 22
• Do you agree with the diagnosis of HHD?
• Do you suspect HCM?
• Do you suspect a different diagnosis and if yes what?
Indeed there are some atypical findings:

For a diagnosis of HHD
- important LVH
- nondilated LV
- Non dilated aorta

For a diagnosis of HCM
- Concentric LVH
- congestive heart failure in the absence of LV obstruction
- or overt end-stage evolution in an old man
Diagnosis of Amyloidotic CMP: ECHO

ED-IVS > 12 mm in the absence of other causes of LV ventricular hypertrophy

Increased thickness of atrioventricular valves

Pericardial effusion

Increased thickness of interatrial septum

Increased thickness of RV free wall

Granular sparkling appearance of ventricular myocardium

Amyloidotic CMP = ○ + at least 2 ○
The diagnostic Work Up progresses.............
$^{99m}$Tc-DPD scintigraphy

Early scan (5 min)  Late scan (3 h)
Right heart catheterization

RA (mean): 14 mmHg

RV: 54/0/14 mmHg

PA: 53/22/35 mmHg

PCWP: 25 mmHg

CO: 5.6 L/min

CI: 2.7 L/min/mq
EMB: cardiac amyloidosis. Severe entity of deposition. Interstitial and endocardial localization. Moderate myocytes damage.
Laboratory & renal bioosy

- Glycemia = 106 mg/dl; HbA1c 6.5
- Serum IgG monoclonal component (mild amount)
  - \( \lambda \) LC: <2.7 mg/L (nv 5.7-26.3)
  - \( \kappa \) LC: 32.5 mg/L (nv 3.3-19.4)
- Search for Bence Jones proteinuria: negative

No amyloidotic deposits in the renal biopsy
At this point the diagnosis is CHF, amyloidotic CMP, probably due to AL amyloidosis.

Do you agree?
No doubt about the diagnosis of amyloidotic CMP.

Indeed there are some atypical aspects for AL amyloidosis:

• no of extra-cardiac involvement
• severe LVH
• LBBB
• no definite prove that amyloidosis infiltrating myocardium is AL
• no definite prove of plasma cell dyscrasia
Diagnostic Work Up still in progresses.............

Etiologic diagnosis of amyloidosis
<table>
<thead>
<tr>
<th>Amyloid protein</th>
<th>Precursor</th>
<th>Syndrome or involved tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>immunoglobulin light chain</td>
<td>Primary / Myeloma associated</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin</td>
<td>Familial (PAF) Senile (wilde type TTR)</td>
</tr>
<tr>
<td>AA</td>
<td>Serum AA</td>
<td>Secondary, reactive</td>
</tr>
<tr>
<td>A β₂M</td>
<td>β₂ microglobulin</td>
<td>Hemodyalisis associated</td>
</tr>
<tr>
<td>AApo All</td>
<td>Apolipoprotein All</td>
<td>Familial</td>
</tr>
<tr>
<td>AFib</td>
<td>Fibrinogen α chain</td>
<td>Familial</td>
</tr>
<tr>
<td>Alys</td>
<td>Lysozyme</td>
<td>Familial</td>
</tr>
<tr>
<td>....</td>
<td>....</td>
<td>....</td>
</tr>
<tr>
<td>Aβ</td>
<td>Aβ protein precursor</td>
<td>Alzheimer’s desease, aging</td>
</tr>
<tr>
<td>APrP</td>
<td>Prion protein</td>
<td>Spongioform encephalopathies</td>
</tr>
</tbody>
</table>
# Etiologic Diagnosis of Cardiac Amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>AL</th>
<th>Hereditary TTR</th>
<th>Wild type TTR (senile)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTR immunostaining</strong></td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>TTR DNA analysis</strong></td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><strong>Plasma cell dyscrasia</strong></td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
…fibrinogen A or TTR mutations identified in 34 / 350 pts (9.7%) previously diagnosed as AL…
Immunohistochemistry: intense positivity for TTR
DNA analysis:
absence of any TTR mutation
(wild type TTR)

WILD-TYPE TTR-RELATED AMYLOIDOTIC CARDIOMYOPATHY
(SENILE SYSTEMIC AMYLOIDOSIS)
Bone marrow biopsy

mild excess of plasma cells (7% of total marrow cellularity)
So the final diagnosis is

wild type TTR (senile) cardiac amyloidosis leading to CHF and PAF in a patient with MGUS and previous systemic hypertension
Questions and point of discussion from the case:

- What is SSA (wtTTR cardiac amyloidosis) ?
- When should be suspected ?
- How to reach the final diagnosis ?
- What is the best treatment ?
- What are the most frequent pitfalls?
- Myopathy with systolic dysfunction ?
Senile systemic amyloidosis

TTR
wild type
General Profile of wt TTR (SSA)

- Male gender
- Average age ~ 70 yrs
- No family history of ATTR
- Heart failure symptoms
- Concentric “LV hypertrophy”
- Mild LV dilatation
- Mild LV systolic dysfunction
- Normal or near normal QRS voltages
Genotypic-Phenotypic Correlation in ATTR

Phenotype

T49A
P64L
G89G
V122I
V30M
A34T
S50A
G47A
A36P
C10A
A34T
P33L
S50A
V41L
H88A
S23A
T60A
L111M
I68L
V122I
SSA

“Neurologic”

“Cardiac”

Phenotype
M.A.C.E. FREE SURVIVAL
(adjusted for multiorgan involvement)

Rapezzi C et al, Circulation 2009:120:1203-1212
DIFFERENTIAL DIAGNOSES

• Hypertensive Heart Disease
• Attr Amyloidosis With Exclusively Cardiac Phenotype
• Hypertrophic Cardiomyopathy (Hcm)
$^{99m}\text{Tc-DPD scintigraphy}$

Early scan (5 min)  Late scan (3 h)
<table>
<thead>
<tr>
<th>Visual cardiac score</th>
<th>Group A TTR-Related CA (15 Patients)</th>
<th>Group B AL CA (10 Patients)</th>
<th>Unaffected Control Patients (10 Patients)</th>
<th>p Value (Kruskal-Wallis Test/Contingency Tables)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>1 (0%)</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (30%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (80%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

**Control**

**AL**

**ATTR**

**SSA**

*JACC 2005;46:1076-1084*
Early Diagnosis of TTR-Related Cardiac Amyloidosis
### 99mTc-DPD scintigraphy: VISUAL SCORE

<table>
<thead>
<tr>
<th>Visual score</th>
<th>SSA (n=30)</th>
<th>ATTR (n=14)</th>
<th>Other CMPs * (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>30%</td>
<td>36%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>70%</td>
<td>64%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Sarcomeric HCM = 9 pts  
  Anderson-Fabry disease = 1 pt  
  HHD = 4 pts
$^{99mTc}$-DPD scintigraphy: SEMIQUANTITATIVE ANALYSIS

Heart retention (%)

- SSA
- ATTR
- Non amyloid CMP

Heart/Whole Body retention ratio

- SSA
- ATTR
- Non amyloid CMP

N.S.

$p < 0.001$
Patients older than 65 yrs and severe unexplained concentric LV hypertrophy and non-dilated LV

**PLASMA-CELL DYSCRASIA?**

- **YES**
  - Consider **AL AMYLOIDOSIS**

- **MGUS?**

- **NO**
  - **99mTc-DPD SCINTIGRAPHY**
    - **MILD myocardial uptake**
      - Consider HCM or other CMPs
    - **ABSTENT myocardial uptake**
      - **TTR gene mutations**
        - **NO**
        - **SSA**
        - **YES**
          - **ATTR**
Amyloid Heart Disease: Therapeutic Strategies

**AL**
- Chemotherapy
- High dose chemotherapy
- Autologous stem cell transplantation
- Heart transplantation

**Hereditary ATTR**
- Liver transplantation
- Heart & liver transplantation
- "new stabilizer drugs" (TAFAMIDIS; Pfizer)

**wt TTR**
Some take home messages:

- SSA is an underdiagnosed entity which raises differential diagnosis problems with HCM and hypertensive heart disease.

SSA should be suspected in every elderly man with unexplained LVH and non-dilated LV. The clues for diagnosis are: Tc-99-M scintigraphy, immunohistochemical analysis of myocardial histology, and exclusion of TTR gene mutations.

- Low QRS voltages are not the rule in cardiac amyloidosis.
- LBBB is a relatively frequent finding in patients with TTR-related amyloidosis.
- LBBB is not frequent in HCM except in the cases with end-stage evolution.

MGUS occurs in up to 5% of elderly people and can represent a pitfall in the diagnostic work-up of amyloidosis.

A generic diagnosis of "cardiac amyloidosis" is not enough; a tissue (etiologic) diagnosis is mandatory. Tc-99-M scintigraphy is an extraordinary non-invasive diagnostic tool, highly sensitive and specific for the diagnosis of TTR-related CMP.
Back up slides
HCM

AMYLOIDOTIC CMP

Rapezzi C et al, Circulation 2009 (in press)
# MAIN ECG FINDINGS OF 233 PTS WITH AMYLOIDOTIC CMP

<table>
<thead>
<tr>
<th></th>
<th>AL (n=157)</th>
<th>SSA (n=15)</th>
<th>ATTR (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB, n (%)</td>
<td>6/146 (4)</td>
<td>6 (40)</td>
<td>4/60 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total QRS score, mV</td>
<td>92 ± 36</td>
<td>120 ± 37</td>
<td>112 ± 34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low QRS voltage, n (%)</td>
<td>88/146 (60)</td>
<td>6 (40)</td>
<td>15/60 (25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Rapezzi C et al, Circulation 2009:120:1203-1212
## Frequency of ECG abnormalities in HCM

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ECG</td>
<td>47 (6)</td>
<td>6 (6)</td>
<td>/</td>
<td>11 (8)</td>
</tr>
<tr>
<td>LVH</td>
<td>484 (58)</td>
<td>66 (65)</td>
<td>/</td>
<td>79 (77)</td>
</tr>
<tr>
<td>Low voltages</td>
<td>31 (4)</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Pseudo-necrosis</td>
<td>294 (35)</td>
<td>35/99 (35)</td>
<td>139 (49)</td>
<td>44 (43)</td>
</tr>
<tr>
<td>Giant - T waves</td>
<td>194 (23)</td>
<td>24 (24)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Giant + T waves</td>
<td>131 (16)</td>
<td>18 (18)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>RBBB</td>
<td>59 (7)</td>
<td>6 (6)</td>
<td>21 (7)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>LBBB</td>
<td>49 (6)</td>
<td>3 (3)</td>
<td>29 (10)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>LAH</td>
<td>138 (16)</td>
<td>/</td>
<td>/</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Abn. Repolariz.</td>
<td>664 (79)</td>
<td>/</td>
<td>/</td>
<td>108 (80)</td>
</tr>
<tr>
<td>ST depression</td>
<td>502 (60)</td>
<td>/</td>
<td>152 (53)</td>
<td>/</td>
</tr>
<tr>
<td>ST elevation</td>
<td>273 (32)</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>
# Standard ECG and prognosis in HCM

<table>
<thead>
<tr>
<th>Studies, yr</th>
<th>N.</th>
<th>Variables</th>
<th>End-points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various AA, 1998-2003</td>
<td>&gt;300</td>
<td>QT dispersion</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Maron, 2005 (Rochester USA)</td>
<td>448</td>
<td>ECG voltages</td>
<td>HCM-rel death</td>
<td></td>
</tr>
<tr>
<td>Conte, 2007 (Turin ITALY)</td>
<td>241</td>
<td>QRS duration</td>
<td>C.V. death</td>
<td>+</td>
</tr>
<tr>
<td>Maron, 2009 (Rochester USA)</td>
<td>330</td>
<td>QRS duration, abnormal Q, QTc, QT dispersion *</td>
<td>Appropriate ICD discharge</td>
<td></td>
</tr>
<tr>
<td>Ommen, 2009 (Rochester USA)</td>
<td>2350</td>
<td>Abnr vsl Normal ECG</td>
<td>Cardiac death</td>
<td>+</td>
</tr>
</tbody>
</table>
Echocardiographic “HCM phenotype” associated with LV hypokinesia (and dilatation) is an age-specific “red flag” which can orient the diagnosis toward different specific etiologies.
Diseases Associated With “HCM and hypokinetic-dilated LV”

- HCM
- Hereditary Amyloidosis
- SSA
- Pompe
- Mitochondrial
- Fabry
- Danon