Cardiac amyloidosis: diagnosis, monitoring and management

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OVERVIEW

• What is Amyloidosis?
• Types of Amyloidosis
• Imaging modalities used in diagnosing cardiac amyloidosis
• Treatment of Amyloidosis
• Treatment of Heart Failure due to Amyloidosis
• Monitoring of Amyloidosis

Amyloidosis and amyloid fibrils

Disorder of protein folding
Structurally diverse precursor proteins adopt an abnormal fibrillar conformation
Bind Congo red and SAP
Unusual stability
Damage tissue structure and organ function

TYPES OF AMYLOIDOSIS.

Amyloid deposits
Fibril precursor proteins in systemic amyloidosis:
• Monoclonal Ig light chains AL
• Serum amyloid A protein AA
• B2 microglobulin Dialysis related amyloid
• Genetically variant proteins Hereditary amyloid
• Transthyretin Senile systemic amyloidosis
Types of Amyloidosis

- Hereditary: 12%
- AA: 15%
- Senile TTR: 2%
- Unclear: 2%
- AL: 59%
- Localised: 10%

>3000 patients seen at NAC since 1990

AL amyloidosis

Extracellular deposition of monoclonal immunoglobulin light chains in an abnormal fibrillar form

Commonest type of systemic amyloidosis

Median survival 6-15 months

- 1 in 1500 deaths in UK

Hereditary Amyloidosis

- Transthyretin (TTR)
- FibA
- ApoA1
- Lys
- Gel
- ApoA2

Transthyretin Amyloidosis

- Plasma protein, tetrameric structure
- Synthesis: hepatic > 95%, choroid plexus, retina
- Carrier protein - role in Vit A metabolism, binds thyroxine

- Familial Amyloid Polyneuropathy (FAP) or hereditary ATTR.
- Wild-type TTR or Senile Systemic Amyloidosis (SSA) - amyloid fibril protein in 25% of individuals > 80 years.
Of 444 patients with diagnosis of ATTR between 1990 and 2011 -

- 292 (66%) hereditary ATTR
  - 207 (71%) male
- 152 (34%) wild-type ATTR (senile systemic ATTR)
  - 144 (95%) male
- Cardiac presentation in 352 (79% of total cohort)
- Current patients under follow-up
  - ~80 hereditary
  - ~80 SSA

DIAGNOSIS OF CARDIAC AMYLOIDOSIS.

TTR Cardiac Amyloidosis

- HISTORY
  - Carpal tunnel syndrome
  - Neuromyological disease
  - Sensorimotor peripheral neuropathy
  - Unexplained intense myalgia and burning sensations
  - Autonomic dysfunction (erecile dysfunction, diarrhoea alternating with constipation), dyshidrosis
  - Vitreous humour opacity

- EXAMINATION

AL Cardiac Amyloidosis

- HISTORY
  - Macroglossia
  - Easy bruising
  - “Panda eyes”
  - Heart Failure symptoms

- EXAMINATION

ECG
- NT-proBNP and TROPONIN
- ECHOCARDIOGRAM
- CARDIAC MR
- 99Tc-DPD MYOCARDIAL UPTAKE SCAN
- BIOPSY
TYPICAL ECGs

Normal Cardiac AL Amyloidosis

ATTR

DIAGNOSIS OF CARDIAC AMYLOIDOSIS

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Biomarkers

- Troponin T

BNP
Methods

- Serum Cardiac Troponins and NT-Terminal Pro-BNPar

Results

- Risk stratification in cardiac TTR amyloid

![Graph showing Kaplan-Meier survival curves for different stages of amyloidosis.](image)

- Stage 1: Red line, p<0.0001
- Stage 2: Blue line
- Stage 3: Black line

- NT-ProBNP and TROPONIN

- ECHOCARDIOGRAM

- CARDIAC MR

- 99Tc-DPD MYOCARDIAL UPTAKE SCAN

- BIOPSY

Biomarkers in risk stratification – NT-ProBNP

<table>
<thead>
<tr>
<th>Status</th>
<th>Alive (%)</th>
<th>Dead (%)</th>
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<tr>
<td>No Response</td>
<td>75%</td>
<td>25%</td>
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<tr>
<td>PR + no BNP</td>
<td>55%</td>
<td>45%</td>
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<tr>
<td>PR + BNP</td>
<td>4%</td>
<td>96%</td>
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<td>CR</td>
<td>4%</td>
<td>96%</td>
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Normal Cardiac AL Amyloidosis

Complex contraction of LV
- Longitudinal Contraction
- Radial Contraction
- Long Axis Deformation
- Twisting

Apex relatively fixed

Normal Cardiac AL Amyloidosis
**Cardiac Amyloidosis**

**Diagnosis of Cardiac Amyloidosis:**
- ECG
- NT-proBNP and TROPONIN
- ECHOCARDIOGRAM
- **CARDIAC MR**
  - **99Tc-DPD MYOCARDIAL UPTAKE SCAN**
  - BIOPSY

**Cardiac MR**
CMR interstitial expansion: amyloid deposition

MRI cine: Amyloidosis

DIAGNOSIS OF CARDIAC AMYLOIDOSIS.
- ECG
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- $^{99}$Tc-DPD MYOCARDIAL UPTAKE SCAN
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$^{99}$Tc-DPD myocardial uptake scan
- Tc-DPD – bone tracer
- Patient scanned at 5 mins and 3 hours post injection
- Similar radiation dose to traditional bone scan
Figure 2 Cardiac and diffuse soft tissue uptake of 99mTc-DPD. (a) A patient with AL amyloidosis showing grade 1 myocardial uptake and minimal uniform soft tissue deposition. (b) Grade 2 cardiac uptake in a STTR patient with TTR pattern of diffuse soft tissue uptake including deltoid, gluteal and abdominal wall muscles (arrows). (c) Grade 3 cardiac uptake in STTR patient with extensive soft tissue uptake (including abdominal wall) and no bony uptake.

Hutt DF et al, EANM, Birmingham, 2011

DPD Scintigraphy

- Grade of uptake appeared to correlate with other clinical features

HISTOLOGICAL DIAGNOSIS – GOLD STANDARD

Cardiac biopsy stained with Congo red and immunohistochemistry showing immuno-specific staining with anti TTR antibodies demonstrating that the amyloid deposits are derived from transthyretin

Supportive Treatment

Over the past 5 years patient survival in AL amyloidosis has improved, attributable to:

1. Advances in treatments that cause reduction in the supply of fibril precursors – e.g. chemotherapy
2. Better supportive care from Specialist HF nurses
Treatment of heart failure - Drugs

- Diuretics form the mainstay of treatment:
  - Furosemide is often the first diuretic to be prescribed. It is high ceiling – i.e. the dose can be increased ++ (40mg a day up to 500 mg a day)
  - Other diuretics such as MRA Spironolactone can be added to increase the effect (usually at dose of 25mg to 50mg)
  - Monitoring diuretics
  - Blood pressure and weight
  - Blood tests – U+Es
  - Sometimes oral therapy is not sufficient and the diuretics are given by injection / infusion in hospital for a few days
  - Many of the drugs prescribed in other common types of heart disease are not helpful in cardiac amyloidosis.
    e.g. ACEI/ARB and betablockers merely reduce the already low blood pressure in patients with cardiac amyloidosis, and can actually worsen symptoms. Avoid Digoxin.

Monitoring of heart rhythm

Summary

- Amyloidosis is a rare complex disease which is increasingly being recognised
- New techniques emerging to diagnose cardiac amyloidosis
- New treatments leading to improved survival
- New monitoring techniques hopefully will improve things further
- Thank you.

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