Amyloidosis

The Cardiologist`s Perspective and more!

Dr. med. Michele Martinelli, Universitätsklinik für Kardiologie Inselspital Bern
Protein Misfolding Disease

Amyloid Fibrils
## Outline of the 4 Main Types of Systemic Amyloidosis

<table>
<thead>
<tr>
<th>Type of Amyloidosis</th>
<th>Source of Amyloid Production</th>
<th>Major Organ Involvement</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (Light chain-associated)</td>
<td>Bone marrow (Light chains produced by plasma cells).</td>
<td>Kidney. Heart. Nervous system. Soft tissue. Liver. GI system.</td>
<td>May be associated with multiple myeloma, but more commonly is not. Treated with chemotherapy.</td>
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<tr>
<td>TTR (Mutant transthyretin-associated)</td>
<td>Unstable mutant transthyretin, produced in the liver.</td>
<td>Nervous system. Heart.</td>
<td>Autosomal dominant inheritance, with a high degree of penetrance. Over 80 mutations, with various patterns of organ involvement. Treated by liver transplant, to remove source of mutant protein production.</td>
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<tr>
<td>AA Amyloid A</td>
<td>Circulating inflammatory protein (serum amyloid A)</td>
<td>Kidney. Liver.</td>
<td>Associated with chronic inflammatory conditions, such as juvenile rheumatoid arthritis, ankylosing spondylitis, chronic infection. Uncommon in USA. Treatment is treatment of underlying condition.</td>
</tr>
</tbody>
</table>

### Cardiologist View

**AL (λ > κ) > 55 %**

**ATTR 40 % (growing ATTRwt!)**

**Serum Protein A < 5% (mainly kidneys)**
Figure 2. Myocardial biopsy in cardiac amyloidosis viewed under electron microscopy. At the lower portion of the figure is the edge of a myocyte; above it is a mass of amyloid fibrils.
Multidisciplinary approach wanted

HEART (55-75%)
- Fatigue (inability to be active)
- Shortness of breath (dyspnea)
- Irregular heart beat
- Fainting (syncope)
- Leads to congestive heart failure

KIDNEYS (60-80%)
- Large amounts of protein in urine (proteinuria)
- Swelling of feet and legs
- End stage kidney disease
- Transplant can be required

PERIPHERAL NERVES (20-45%)
- Neuropathy
- Impotence
- No temperature sensation in hands and feet

OTHER ORGANS
- Liver (15-30%)
- GI Tract (5-16%)
- Eyes (10-25%)
- Tongue (~10%)
- Soft Tissue (20-35%)
HEART (55-75%)
- Fatigue (inability to be active)
- Shortness of breath (dyspnea)
- Irregular heart beat
- Fainting (syncopy)
- Leads to congestive heart failure
The clinical progression of cardiac amyloidosis

**Preclinical**
‘asymptomatic’
- LVH
- Elevated BNP
- Abnormal ECG
- Pericardial effusion

**Early Symptomatic**
Impaired exercise tolerance
- LVH, with ‘normal’ LV systolic function
- Small LV cavity
- Diastolic dysfunction
- Impaired cardiac reserve

**Advanced**
Severely limited functional capacity
- Syncope
- Right and left heart failure
- LVH, with reduced LV systolic function
- Reduced atrial mechanical activity

** ATTR familial, systemic senile: Years**
**AL amyloid: variable - months to years**
Survival According to Cardiac Status

You see patients very late, time is running out specially for AL Amyloidosis

Cardiac involvement

Percent Surviving

Years after treatment initiation

n=137 median 1.6 yrs

n=175 median 6.4 yrs

You can refer to Ann Intern Med. 2004;140:85-93.
Serum Troponin and BNP predict outcome in AL Amyloidosis

Elevations in BNP, troponin predict worse prognosis

– Stage I: NT-BNP < 332 ng/L, cTnT < 35 ng/L;
– Stage II: either above threshold
– Stage III: both above threshold

Dispenzieri et al., 2004, J Clin Onc
Clinical presentations of cardiac amyloidosis

• Exertional Fatigue
• Unexplained ventricular hypertrophy
• HFpEF Diastolic dysfunction
• Left and Right Heart Failure
• Syncope / Stroke with Afib
• ‘typical’ ECG abnormalities
  – low voltage
  – Pseudo-infarct pattern
ECG (low voltage <0.5mV)! Not all have low voltage! AL 45% of patients, ATTR 25% of patients), Pseudoinfarction
Echo
Diastolic Dysfunction (HFpEF)
Wall thickness
Myocardial «Sparkling»
Valve thickening
*Strain (apical sparing)*
Pericardial effusion
Global subendocardial late enhancement pattern

Abnormal T1 Gadolinium Kinetics (abnormal earlier myocardial nulling (myocardium brighter than blood))

J Am Heart Assoc. 2012;1:e000364
TypingAmyloidosis

AL Amyloidosis
Chemotherapy
Anti Fibril Therapy

ATTR Amyloidosis f, wt
Anti Fibril Therapy
Liver Transplantation
To find amyloidosis you have to know how to look for it

**Typing process**

**Histology:** Staining Kongo red, African blue, Polarisation (errors in the preparation, staining or viewing possible)

**Immunohistochemistry:** Anti-Fibril Protein Antibodies

**Proteomics** laser microdissection and mass spectrometry *(future gold standard?)* typing of protein and protein fragments nearly 100% diagnostic, but expensive)

**Genetic Testing** fATTR and other forms of Amyloid
Screening tests for AL Amyloidosis

- Monoclonal protein testing of the serum and urine (FLC κ, λ, serum and urine protein electrophoresis and immunofixation)

- If known MGUS look for NTproBNP >330 ng/L, Troponin Leak and Albuminuria > 0.5g/ (Progression to Amyloidosis 8-9%/Year, Progression to Malignancy 1%/Year)

**Free Light Chain (FLC):**

- Kappa 3.30 - 19.40 mg/l
- Lambda 5.70 - 26.30 mg/l
- Ratio Kappa/Lambda 0.26 - 1.65

Modified for renal insufficiency: Ratio 0.37-3.1

www.wikilite.com
In international Cohort with ATTR amyloid, whose median age was 75 years, 19% had a detectable monoclonal protein using these very sensitive techniques.

*Circulation. 2016;133:2404-2412*
Patient C

Clinical work up:

High suspicion (Echo, MRI) for isolated cardiac amyloidosis Type ATTR wt

If you have three choices:

a) Cardiac biopsy
b) 99m Tc-labeled DPD Scintigraphy
c) Mass spectrometry of Fat Biopsy
Heart with pos. «Bone» Scan
“the combined findings of grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy and the absence of a monoclonal protein in serum or urine had a specificity and positive predictive value for cardiac ATTR amyloidosis of 100%”
Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/or cardiac magnetic resonance imaging (CMR) suggesting/indicating cardiac amyloid.

Bone scintigraphy with $^{99m}$Tc-DPD/HMDP/PYP

- Grade 0
- Grade 1
- Grade 2 to 3

Serum immunofixation + Urine immunofixation + serum free light chain assay (Freelite)

Monoclonal protein present?

- No
- Yes

- Cardiac AL/ATTR amyloidosis unlikely
- Review/request CMR

Need specialized assessment for Diagnosis:
Histological confirmation and typing of amyloid

- Yes
- No

- Cardiac ATTR amyloidosis
- TTR genotyping

Cardiac amyloidosis (AL/AAPoAI/ATTR/other)

Variant ATTR amyloidosis

Wild-Type ATTR amyloidosis
Amyloidogenic TTR Cascade

Liver → TTR Tetramer → TTR Monomer → Misfolded State → Amyloid Fibril

- Suppression of Amyloidogenic TTR
- TTR Stabilization
- Fibril Degradation

<table>
<thead>
<tr>
<th>TTR THERAPEUTIC DRUG CLASS / DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>POTENTIAL RISKS</th>
<th>PIPELINE STAGE</th>
<th>ROUTE</th>
<th>DOSING</th>
<th>DRUG COMPANY</th>
</tr>
</thead>
<tbody>
<tr>
<td>SILENCERS</td>
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<td>ASO</td>
<td>Suppresses hepatic TTR mRNA and serum TTR levels.</td>
<td>Injection site reaction</td>
<td>Phase 3</td>
<td>IV/SQ</td>
<td>300 mg</td>
<td>ISIS</td>
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<tr>
<td>siRNA</td>
<td>Small interfering RNA bound to the RNA-induced silencing complex mediates the cleavage of target messenger RNA. Delivery agents include lipid nanoparticles (ALN-TTR01, ALN-TTR02) and GalNAc conjugation (ALN-TTRSC).</td>
<td>Injection site reaction; LFT changes; Monocytosis</td>
<td>Phase 3</td>
<td>IV/SQ</td>
<td>5 or 7.5 mg/kg QD x5 days, QWK x5 weeks</td>
<td>Argenx</td>
</tr>
<tr>
<td>STABILIZERS</td>
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<tr>
<td>Tafamidis</td>
<td>Binds to thyroid-binding sites of the TTR tetramer, inhibiting dissociation into monomers and blocking the rate-limiting step in the TTR amyloidogenesis cascade</td>
<td>Urinary tract infection, diarrhea, abdominal pain</td>
<td>Phase 3</td>
<td>Oral</td>
<td>20 mg QD</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>NSR/ID: Binds and stabilizes common familial TTR variants against acid-mediated fibril formation</td>
<td>COX enzyme-related volume overload, GI bleeding, renal dysfunction</td>
<td>Phase 3</td>
<td>Oral</td>
<td>250 mg BID</td>
<td>Merck</td>
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<tr>
<td>DEGRADERS</td>
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<td>Doxycycline-TUDCA</td>
<td>Removes already-deposited amyloid.</td>
<td>Under investigation</td>
<td>Phase 2</td>
<td>Oral</td>
<td>100 mg BID/250 mg TID</td>
<td>West-Ward</td>
</tr>
<tr>
<td>Monoclonal anti-SAP Antibodies</td>
<td>Antibody against a normal non-fibrillar glycoprotein SAP, promotes a giant cell reaction that removes visceral amyloid deposits</td>
<td>Infusion site reaction</td>
<td>Phase 1</td>
<td>IV</td>
<td>To be determined</td>
<td>GSK</td>
</tr>
</tbody>
</table>

ASO = antisense oligonucleotides; TTR = transthyretin; NSADI = non-steroidal anti-inflammatory drug; COX = cyclooxygenase; TTR-WT = transthyretin wild type; TUDCA = tauroursodeoxycholic acid and doxycycline; SAP = serum amyloid P component; iv = intravenous injection; ASO = anti-sense oligonucleotides; mRNA = messenger RNA; SQ = subcutaneous injection; GalNAc = triamteric N-acetylgalactosamin.
Dr. med. M. Martinelli, Universitätsklinik für Kardiologie Inselspital Bern

«Natural» Degraders

Curcumin (Gelbwurz)

Greentea Epigallocatechin-3-gallate

2 Kapseln pro Tag

Verbraucherinformation
praevent-loges®
Nahrungsergänzungsmittel

Mit Grüntee-Extrakt und Vitamin C

Verzehrmögliche: 2-mal 1 Kapsel täglich vor den Mahlzeiten

Pakungen: Packungen mit 30 und 100 Kapseln

Bitte beachten Sie:

Zutaten:

- Grüntee-Extrakt
- Vitamin C
Supportive care in Cardiac Amyloid patients

- Fluid intake, Salt intake, Diuresis management!
- Neurohormonal antagonists (ACEI/ARB, B-blockers) are often poorly tolerated
- Aldosterone antagonism is usually tolerated
- For atrial and ventricular arrhythmias – amiodarone
- Digoxin in low doses for Afib rate control appears safe
- Encourage physical activity
Network for Amyloidosis!

Thank you

Michele Martinelli, Bern