Transthyretin (ATTR) Amyloidosis: tricks and treats

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Chicago IL
### Inherited Amyloidoses

<table>
<thead>
<tr>
<th>Subunit</th>
<th>Type</th>
<th>Source</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transthyretin</td>
<td>ATTR</td>
<td>Liver</td>
<td>PN/ANS, heart, GI, rarely kidney</td>
</tr>
<tr>
<td>Apolipoprotein Al/AlI</td>
<td>AApoAl/AlI</td>
<td>Liver/GI</td>
<td>Kidney, heart, PN (Al)</td>
</tr>
<tr>
<td>Fibrinogen Aα chain</td>
<td>AFib</td>
<td>Liver</td>
<td>Kidney</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>ALys</td>
<td>GI tract</td>
<td>Kidney, liver, spleen</td>
</tr>
<tr>
<td>Gelsolin</td>
<td>AGel</td>
<td></td>
<td>Cranial neuropathy/lattice dystrophy</td>
</tr>
</tbody>
</table>

- Autosomal dominant genetics
- Slow clinical progression
- Solid organ transplantation
Transthyretin (TTR)

- 127 amino acid chain
- Primarily produced by liver (eye, brain)
- > 120 TTR mutations (amino acid substitutions)
- Untreated, people live 7-15 YRS after presentation
- Affects ~10-15,000 world-wide
## Mutant (ATTRm) vs Wild-type (ATTRwt)

<table>
<thead>
<tr>
<th></th>
<th>ATTRm</th>
<th>ATTRwt</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR Protein</td>
<td>Abnorm</td>
<td>Norm</td>
</tr>
<tr>
<td>Onset Age (YRS)</td>
<td>30-75</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Female</td>
<td>40%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Carpal Tunnel</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Auto Neuropathy</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Periph Neuropathy</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>GI Motility</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Survival (YRS)</td>
<td>7-15</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
Nomenclature for ATTRm

Abbreviation: V30M ATTR
Penetrance: Will I get the disease?

77 Swedish families
235 affected
1353 family members

Age of Onset in ATTRm

B = T60A
R = V30M
G = V122I

Zhen DB et al. Clin Genet 2015; 88:396
Most prevalent ATTRm in the USA

- V30M  Peripheral neuropathy
- T60A  Heart/Peripheral neuropathy
- V122I Heart/Peripheral neuropathy
- L58H  Soft tissue/PN/Heart
- S77Y  Heart/PN/Soft tissue
- I84S  Heart/PN
- T49P  PN/Heart/Soft tissue
ATTRm Spectrum of Disease

Peripheral    Autonomic    Leptomeningeal    Heart

Val30Met     Thr49Pro     Leu12Pro     Val122Ile
Leu58His     Glu42Gly     Asp18Gly     Thr60Ala
Thr60Ala     Thr60Ala     Leu55Arg     Ser77Tyr
Phe64Leu     Phe44Ser     Phe64Ser     Ile84Ser
Ala97Ser     Ser50Arg     Tyr114Cys     Val30Ala

His90Asp
Peripheral Nervous System

- Ascending numbness, etc.
- Cold insensitivity
- Muscle weakness
- Stork walk (steppage gait)
- Inability to rise from seat
- Muscle atrophy
Autonomic Nervous System

- Dry eyes, mouth
- Altered sweating
- Blunted heart rate
- (near) blackouts
- Diarrhea/constipation
- Bladder dysfunction
- Erectile dysfunction
ATTRm: How many are we?

World wide ~10-15,000

United States

1:million to 1:100,000
300 to 3,000 Dx

African-Americans (3.9%)

>65 year old (3-4%)

~1.4 million gene (+)

90,000-135,000 gene (+)

ATTR cardiomyopathy (7%)

<10,000
# ATTRwt: How many are we?

## Sweden
- 85 consec autopsies >80 yo
  - LV involvement: 16%
  - Significant amyloid: ~8%
- 25% hearts (+) ATTR

## Finland
- 256 autopsies
- TTR amyloid: 25%
- Mod/Severe amyloid: 5.5%

## US 2010 Census
- Men >80 years: 4.08 million
- ATTR cardiomyopathy: ~ 250,000 men (6.5%)
Amyloid Treatment Strategies

• prevent protein misfolding

• suppress amyloidogenic protein production

• destabilizing amyloid deposits