Diagnosis of Amyloidosis

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Amyloid: what is it and why it forms

Name = misnomer: “amyloid” means starch* but deposits of amyloid contain predominantly protein which became mis-folded

Amyloidoses = amyloid diseases

* the name amyloid comes from the early mistaken identification by Rudolf Virchow (XIX century) of the substance as starch based on crude iodine-staining techniques

amylum = starch in Latin, ἄμυλον amylon = starch in Greek

* the name amyloid comes from the early mistaken identification by Rudolf Virchow (XIX century) of the substance as starch based on crude iodine-staining techniques
Amyloidoses – protein folding disorders

α helix

β pleated sheet

Fibrillogenesis
Conformational shift to
β-pleated sheet 2^0 structure

hydrophobic, insoluble
non-functional
resistant to degradation
sticky (prone to aggregation)
extracellular
affinity to Congo red stain
fibrillar (by electron microscopy)

Congo red positivity
with green birefringence
under polarized light

amyloid binding sites
Amyloidoses – protein folding disorders

protein quality control systems:
intracellular (proteasomes*)
extracellular (macrophages)

Increased concentration
Intrinsic instability
Proteolytic cleavage

mutations
Older age
proteotoxicity

precursor protein
misfolded protein
protofibril
mature fibrils

Proteasomes = protein complexes which degrade unneeded or damaged proteins by proteolysis
Proteasomes are part of a major mechanism by which cells degrade misfolded proteins
Pathogenesis of hereditary amyloidosis

Hereditary: ATTR, AFib, AApoAl, All, C-III...

Amyloidosis derived from transthyretin: ATTR
- The most common hereditary amyloidosis in the US
- TTR circulates as tetramer,
- transport of thyroxin & retinol (vitamin A)
- inherited mutation destabilizes tetramer
- >95% liver; choroid plexus, eye
- >100 mutations
Hereditary: ATTR

Amyloidosis derived from transthyretin: ATTR

- polyneuropathies (sensory, autonomic), cardiac, gastrointestinal, some kidneys

The most common hereditary amyloidosis in the US

~4% of African Americans (TTR V122I)

Variable penetrance
Late onset in some
Family history often missing

Can MIMICK AL – danger of misdiagnosis

- Carpal tunnel bilateral
- Enlarged heart
- Peripheral nerve with amyloid deposits

* deposits of amyloid
ATTRwt (wild type):

normal (wild type) transthyretin is prone to fibrillogenesis at older age. Protein quality control systems are less effective at older age...

- cardiac amyloid at old age
  “cardiac Alzheimer”
Formerly SSA: senile systemic amyloidosis in males, under-diagnosed – 25% of octogenarians risk factors? prevention?
How to diagnose amyloidosis?

1. Detection:
   - **ALL** amyloids are Congo red positive

2. Typing of amyloid protein
DIAGNOSIS:

kidney, cardiac, peripheral nerves, other sites

laboratory tests to support the diagnosis but not to make it

Routine stain: extracellular “amorphous” deposits, not-specific for amyloid

Diagnosis = Congo* red stain with green birefringence under polarized light [“apple green” birefringence]

Amyloid is fibrillary only by electron microscopy

* the name “Congo” was given for marketing purposes but the stain has NO origins in African river
Differential diagnosis of proteinuria/nephrotic syndrome in adults:
1. Focal and Segmental Glomerular Sclerosis/Minimal change disease
2. Membranous nephropathy
3. Diabetes
4. Amyloidosis!!!

Cardiac amyloidosis – heart failure, arrhythmia, long list of differential
differential Polyneuropathy – sensory and autonomic disturbances, long list of differential
Amyloid deposits are unevenly distributed in tissues
Amyloid can be detected in subcutaneous fat

Fat biopsy typically from periumbilical abdomen ("surrogate site")
for diagnosis and screening of patients at risk
Amyloid detection in fat:

Sensitivity highly variable 54-93%  
Specificity: 93-100%

Affected organ – best yield
Fine et al, 2014:
ATTR, cardiac versus non-cardiac tissue sampling:

<table>
<thead>
<tr>
<th>biopsy</th>
<th>all</th>
<th>Familial ATTR</th>
<th>Wild type senile ATTR</th>
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<tbody>
<tr>
<td>Fat aspirate</td>
<td>225/106+ 47%</td>
<td>141/94+ 67%</td>
<td>84/12+ 14%</td>
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<tr>
<td>Bone marrow</td>
<td>164/60+ 37%</td>
<td>100/41+ 41%</td>
<td>64/19+ 30%</td>
</tr>
<tr>
<td><strong>heart</strong></td>
<td><strong>131/131+ 100%</strong></td>
<td><strong>42/42+ 100%</strong></td>
<td><strong>89/89+ 100%</strong></td>
</tr>
<tr>
<td>Sural nerve</td>
<td>54/45+ 83%</td>
<td>54/45+ 83%</td>
<td>0</td>
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Fat aspiration was the most commonly performed followed by bone marrow biopsy. Other: rectum, kidney, carpal ligament, liver, small intestine, sural nerve
Pathology of Familial amyloidoses:

1. Detection of amyloid in the index patient
   - lack of a family history
   - new mutation
2. Screening of family members/known carriers
3. Staging, organ involvement
Thank you
Questions?
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Early diagnosis of amyloidosis = biggest challenge

Increased awareness and education

Clinical suspicion...
Pathologic suspicion... second opinion

Patients’ perspective...