Familial Amyloidosis
Yesterday, today, and tomorrow

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Familial Amyloidosis Support Group Meeting
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Yesterday, today, tomorrow...

- **Yesterday**
  - History and nomenclature
  - Making the correct diagnosis
  - What families could expect
Discovery and identification of amyloidosis

1854 Discovery
Virchow VR.
Ueber einem Gehirn and Rueckenmark des Menschen auf gefundene Substanz mit chemischen reaction der Cellulose.

1922 Identification by Congo Red staining
Bennhold H.
Eine spezifische Amyloidfärbung mit Kongorot.
<table>
<thead>
<tr>
<th>Year</th>
<th>Discovery</th>
</tr>
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<tbody>
<tr>
<td>1959</td>
<td>Amyloid fibril ultrastructure identified</td>
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<tr>
<td>1971</td>
<td>Primary amyloid: immunoglobulin light chain</td>
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<tr>
<td>1972</td>
<td>Secondary amyloid: subunit of the acute phase SAA protein</td>
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<tr>
<td>1981</td>
<td>Familial amyloid: transthyretin (gene mutations)</td>
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Rare forms of familial amyloidosis
Classification of systemic amyloidosis

AL: Immunoglobulin light chain, kappa or lambda
ATTR: Transthyretin, ~100 variant forms cause amyloidosis
Rare familial:
  - AApoo AI Apolipoprotein AI,
  - AApoo AII Apolipoprotein AII,
  - AFib Fibrinogen,
  - ALys Lysozyme,
  - AGel Gelsolin
AA: Portion of serum amyloid A protein (SAA)
Distribution of common systemic types of amyloidosis...

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage of all amyloidoses</th>
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<tbody>
<tr>
<td>AL</td>
<td>80%</td>
</tr>
<tr>
<td>ATTR</td>
<td>10%</td>
</tr>
<tr>
<td>Rare familial</td>
<td>1%</td>
</tr>
<tr>
<td>AA</td>
<td>2%</td>
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Familial (ATTR) amyloidosis

Trans thy retin is a transport protein for thyroid hormone and retinol binding protein

Cause: Autosomal dominant inheritance of a mutant transthyretin gene (100+ known, most cause amyloidosis)

Onset age: 20’s-old age; same within family; onset for women is a little later than for men

Survival: 7-15 years from diagnosis
TTR amyloid pathogenesis...

- transthyretin

- 127 amino acids (building blocks)

Normal TTR → Mutant TTR → amyloid deposits
Autosomal dominant inheritance...

Each child has a 50-50 chance of inheriting the mutant gene
Yesterday, today, tomorrow...

- Yesterday
  - History and nomenclature
  - Making the correct diagnosis
  - What families could expect
Making the correct diagnosis

- Tissue biopsy positive for amyloid
- Look for variant protein and/or gene mutation
Diagnosing the amyloid type...

Fat or Tissue Biopsy (+)

Clinical Features
- ATTR: neuropathy, cardiomyopathy, vitreous opacities
- AL: proteinuria, macroglossia, neuropathy, hepatomegaly

Family History: yes or no

Molecular Genetics
- DNA
- RFLP

Isoelectric Focusing
(+)
(-)

Immunofixation Electrophoresis

Bone Marrow Biopsy

Other Amyloid Diseases

(-)
(+)

Mass spec for sequence variations and post-translational modifications

Light Chain Amyloidosis

TTR Amyloidosis

Other Amyloid Diseases
• Yesterday, today, tomorrow...

• Yesterday
  • History and nomenclature
  • Making the correct diagnosis
  • Disease in patients; impact on families
Case 1

- 33 year old man of came for evaluation in 1976. Had onset of severe neuropathy at age 26 and diagnosis of Charcot-Marie Tooth disease, similar to his mother.
- Sensory loss in legs, arms, chest
- Motor loss with weakness of lower legs; urinary incontinence
- Autonomic neuropathy with orthostasis (BP 80/60 on standing); severe diarrhea and a 30 lb wt loss
Case 1 (con’t)

- Died at age 36 of progressive disease; bed sores, sepsis, malnutrition, renal failure (due to antibiotics).
- Studies on his amyloid protein found familial amyloid to be TTR.

(The prealbumin nature of the amyloid deposits in FAP-Swedish variety, BBRC 99: 1326, 1981)
Case 1, sister

- 4 years younger than her brother, mother of 2 young children; she and husband were farmers
- At age 32 (time of brother’s death) could not wear shoes because feet hurt; had to stop helping with the farm work
- Four years later, when testing available, she was tested for the mutant gene
Yesterday, today, tomorrow

- Diagnostic techniques in place commercially and at specialized centers, but even so, often diagnosis is late
- Major treatment available for some individuals since 1992
- Family impact
Treatment of familial TTR amyloidosis

--- orthotopic liver transplant ---

mutant TTR

normal TTR

Aggressive treatment
Mortality and morbidity risk

Requires: Early disease status
Availability of donor
Yesterday, today, tomorrow...

- Medical knowledge to support early diagnoses and even better, presymptomatic diagnoses.
- Treatment options, some even before disease begins
- Family impact hopefully minimal
ATTR tomorrow...

Diagnosis: IEF screening test and DNA sequencing for at-risk family members

- Important to look for TTR mutation in all Black individuals with cardiomyopathy

Major treatment will have options that will be available worldwide:

1. liver transplantation
2. diflunisal: multicenter international clinical trial in progress
3. FoldRx1006A: multicenter international trial in review
4. more options needed, ALN-TTR
Supportive treatment

1. For heart:
   diuretics; low salt diet; rhythm control, if necessary

2. For peripheral neuropathy:
   medications; active exercises; ankle braces; foot care

3. For autonomic neuropathy: BP and GI
   midodrine for low BP, elastic stockings
   low fat diet, meds for diarrhea, food supplements, etc

4. Genetic counseling: new GINA information
Genetic Information Nondiscrimination Act (GINA)

- 2000 President signed order to protect federal employees from genetic discrimination in employment
- 2008 Congress finally passed GINA
- May 21, 2009 health insurance protection
- November 21, 2009 employment protection
In making decisions about your health insurance or employment, GINA prohibits:

- Using genetic test results on you
- Using genetic tests from a family member,
- Using manifestations of a genetic disease in the family
- Using the participation of you or family in genetic research
Also GINA prohibits....

- Insurers from using genetic information to set health insurance eligibility or premiums
- Insurers from requiring an individual to take a genetic test
- Using genetic information for hiring, firing, or promotions in employment decisions
GINA con’t

• Legislation varies by state in protections provided
• Allows individuals experiencing discrimination to file a civil suit (damages capped at $300,000. plus back pay)
Boston University Amyloid Program