Familial Amyloidosis: What is it? How is it inherited?

Amyloid Support Group Familial Amyloidosis Meeting  
Chicago, Illinois  
Saturday, October 29, 2011

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Boston Amyloid Treatment and Research Center
When was TTR amyloid discovered?

- **1854** Virchow (Germany) Discovery of amyloid in tissue

- **1952** Andrade (Portugal) A peculiar form of peripheral neuropathy (Brain journal)

Dr. Andrade reported an amyloid disease prevalent in one area of northern Portugal. He showed that it was inherited and caused neuropathy in mid-life.
First Symposium, Groningen 1967
First Symposium Proceedings…
1967 1st Symposium on Amyloidosis

- 6 clinical reports: FAP; Secondary (AA); diagnostic tests; 3 reports on amyloid and aging

- Familial amyloidotic polyneuropathy, Dr. Andrade reported 696 cases in 173 families in northern Portugal (Povoa de Varzim)
  - proved the hereditary nature of the disease
  - showed degeneration of peripheral nerves by pathologic examination
  - “no mild cases”
Further studies....

- **1978**  
  Amyloid deposits stained with antibody to prealbumin (TTR)

- **1981**  
  Amyloid fibrils proven to be prealbumin

- **1983**  
  First discovery of prealbumin gene mutation (Val-30-Met)

- **1986**  
  Prealbumin re-named trans thy retin

- **1983-present**  
  More than 100 pathologic TTR mutations discovered
Prealbumin aka transthyretin
Systemic amyloidosis:

- AL: 80%
- Non-AL: 20%
Systemic non-AL amyloidoses

- AA (or secondary) 2%
- Age-related (senile) systemic amyloidosis 2-3%
- Familial forms due to gene mutations
  - ATTR 10-12%
  - Apolipoprotein Al < 1%
  - Apolipoprotein AII < 1%
  - Fibrinogen A alpha < 1%
  - Lysozyme < 1%
  - Gelsolin < 1%
When were rare familial types discovered?

<table>
<thead>
<tr>
<th>Type</th>
<th>Discovery</th>
<th># mutant forms</th>
<th>Clinical feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein AI</td>
<td>Benson, 1988</td>
<td>15</td>
<td>kidney*, liver, heart, skin</td>
</tr>
<tr>
<td>Apolipoprotein AII</td>
<td>Benson, 2001</td>
<td>5 (all stop codons)</td>
<td>kidney</td>
</tr>
<tr>
<td>Fibrinogen Aα</td>
<td>Benson, 1993</td>
<td>9</td>
<td>kidney*, nervous system</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Pepys, 1993</td>
<td>6</td>
<td>kidney*, GI, skin</td>
</tr>
<tr>
<td>Gelsolin</td>
<td>Maury, 1990</td>
<td>2</td>
<td>cranial neuropathy*, cornea, kidney</td>
</tr>
</tbody>
</table>
Making the correct diagnosis

- Tissue biopsy positive for amyloid
- R/O AL and AA amyloidoses
- Confirm tissue type by immunohistochemistry with antibody to specific protein (or mass spec, if avail.)
- Confirm all inherited forms by genetic analysis of patient’s DNA
Diagnostic testing

- Isoelectric focusing: detection of variant TTR protein in serum

- Immunohistochemistry: identification of deposited protein in fat or tissue biopsies

- Genetic analyses: identification of gene mutation

- Mass spectrometry: characterization of TTR variant
Systemic non-AL amyloidoses

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Senile systemic amyloidosis (SSA)

- Caused by wild-type TTR
- Heart predominant organ involved
- Older age; mostly men
- Also called age-related amyloidosis or senile cardiac amyloidosis
SSA diagnosis made by:

- Tissue biopsy positive for amyloid
- Amyloid deposits positive for TTR
- TTR genetic testing negative for a TTR mutation
- Clinical picture of older person, most likely with cardiomyopathy and without multisystem disease
114-year-old Arbella Perkins Ewings, considered the oldest person in Texas, died Saturday at a Dallas retirement home.

At 114, one of Texas' supercentenarians dies

By: Andrew Kreighbaum

Posted: 3/25/08

Genes and lifestyle choices are known to prolong a person's life, but caretakers of the oldest Texan say faith kept her active for more than a century.

Arbella Perkins Ewings of Dallas was 114 years old when she died Saturday. She was one of a small subset of Americans called supercentenarians - people who have exceed the age of 110. Ewings had been living at home before she was moved into a nursing home to receive treatment for a broken hip.

Female supercentenarians are statistically dominant, outnumbering men in the group by as many as 10-to-1. Coles speculated that the XX chromosome structure in a woman's genome may act as a compensation measure. Men only have one X chromosome, and if it is defective he cannot compensate for it as a woman could.

The cause of death of most supercentenarians is TTR-amyloidosis, a failure of a thyroid hormone that controls metabolism and maintains body temperature.
Systemic non-AL amyloidoses

- AA (or secondary) $\quad 2\%$
- Age-related (senile) systemic amyloidosis $\quad 2\text{-}3\%$
- Familial forms due to gene mutations $\quad 10\text{-}12\%$
  - ATTR
  - Apolipoprotein Al $\quad < 1\%$
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Familial (ATTR) amyloidosis: most common familial form

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

Cause: Autosomal dominant inheritance of a mutant transthyretin gene (100+ variants, 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 mutation: V122I

- variant TTR present in 4% of individuals of African ancestry
- associated with cardiomyopathy of late onset
- incidence of disease unknown
TTR-V122I in Black patients with amyloidosis

Connors et al., Am Heart J, 2009
TTR amyloid pathogenesis...

transthyretin

127 amino acids (building blocks)

Normal TTR  Mutant TTR  amyloid deposits
Treatment of familial TTR amyloidosis

- orthotopic liver transplant

mutant TTR | normal TTR

Aggressive treatment
Significant mortality and morbidity risk
Requires: Early disease status & availability of donor
Diagnosis and treatment of ATTR amyloidosis

Diagnosis:

IEF screening test will show variant protein in serum; DNA sequencing necessary for diagnosis of mutation.

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

Major treatment:

- liver transplantation
- diflunisal: multicenter international clinical trial in progress
- Tafamidis (Pfizer) multicenter international trial awaits FDA approval
- ALN-TTR-NT-001 (Alnylam) in clinical trial in Europe
- ISIS
- Other
ATTR 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 Gl
   midodrine for low BP, elastic stockings
   Low fat diet, meds for diarrhea, food supplements, etc

4. Genetic counseling
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## Treatment of rare types of familial amyloidosis

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<th>Prognosis</th>
<th>Treatment</th>
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<tr>
<td>Apolipoprotein AI</td>
<td>Slow to progress</td>
<td>Made in liver (and GI); kidney or kidney/liver transplant</td>
</tr>
<tr>
<td>Apolipoprotein AII</td>
<td>Rare; early (30s); slow to progress</td>
<td>Renal transplant gives favorable results</td>
</tr>
<tr>
<td>Fibrinogen A α</td>
<td>After onset, rapid progression to azotemia</td>
<td>Made in liver; good prognosis with liver transplant</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Slow to progress</td>
<td>Made in PMNs and macrophages; No specific treatment; renal transplant leads to good outcome</td>
</tr>
<tr>
<td>Gelsolin</td>
<td>Slow to progress</td>
<td>No treatment; plastic surgery</td>
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Autosomal dominant inheritance...

Each child has a 50-50 chance of inheriting the mutant gene
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)
Amyloid Treatment & Research Center

Support
- Patients
- Gruss & Wildflower Foundations
- PO1 HL 068705
- RO1 DK 090696
- RO1 AG 031804

Clinical Team
- Amyloid: Skinner, Libbey, Cowan, O’Connell
- Hematology: Seldin, Sanchoyewala, Sloan, Andrea, Lerner, Quillen
- Transplant & Clinical Trials: Finn, Shelton, Brauneis, Fennessey
- Apheresis Program: Quillen
- Pulmonary: Berk
- Cardiology: Ruberg, Meier-Ewert
- Renal: Dember, Stern, Havasi

Research Team
- Gerry Lab: Connors, Spencer, Chan, Prokaeva, Klimtchuk, Koch, Lu
- Amyloid Pathology: O’Hara, Soo Hoo, Kroll, Erdogan, Henderson, Andry
- Transgenics, siRNA, miRNA: Seldin, Ward, Hovey, Shibad, Weng
- MRI: Anderson, Hamilton, Ruberg
- Mass Spec: Costello, Theberge, Hong
- Vickery Trinkaus-Randall, Flora Ren
- Flora Sam
- Ronglih Liao, James Guan