



Familial Amyloidosis Yesterday, today, and tomorrow

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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.

Virchows Arch Pathol Anat 1854;6:135-8.

1922 Identification by Congo Red staining

Bennhold H.

Eine spezifische Amyloidfärbung mit Kongorot.

Munch Med Wochenschr 1922;97:1537-8.

Discovery of systemic amyloidosis types...

- 1959 Amyloid fibril ultrastructure identified
 - 1971 Primary amyloid: immunoglobulin light chain
 - 1972 Secondary amyloid: subunit of the acute phase SAA protein
 - 1981 Familial amyloid: transthyretin (gene mutations)
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:

AApo AI Apolipoprotein AI,

AApo AII Apolipoprotein AII,

AFib Fibrinogen,

ALys Lysozyme,

AGel Gelsolin

AA: Portion of serum amyloid A protein (SAA)

Distribution of common systemic types of amyloidosis...

AL : 80% of all amyloidoses

ATTR : 10% of all amyloidoses

Rare familial: 1% of all amyloidoses

AA : 2% of all amyloidoses

Familial (ATTR) amyloidosis

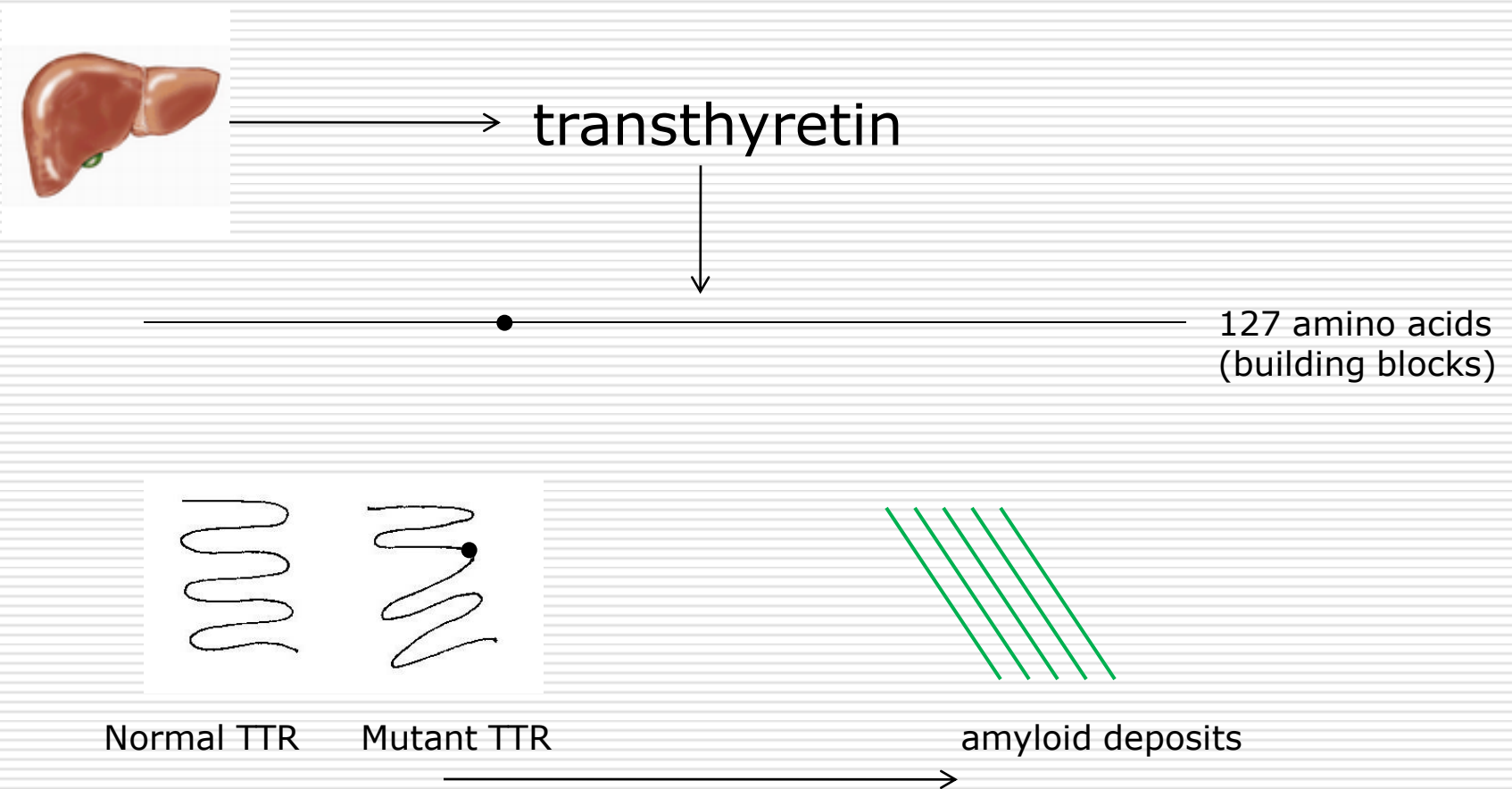
Trans thy retin is a transport protein for thyroid hormone and retinol binding protein

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

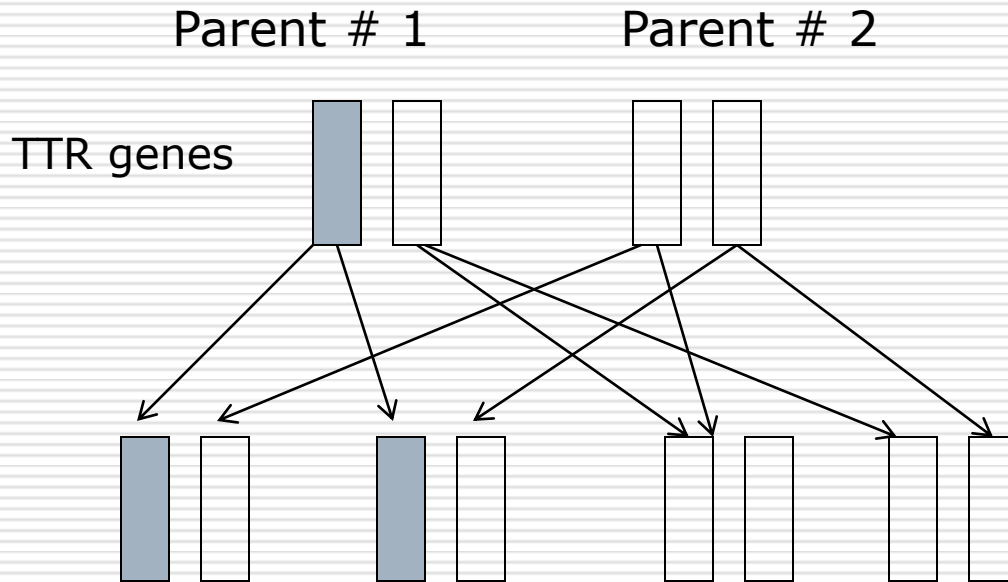
Onset age: 20's-old age; same within family; onset for women is a little later than for men

Survival: 7-15 years from diagnosis

TTR amyloid pathogenesis...



Autosomal dominant inheritance...



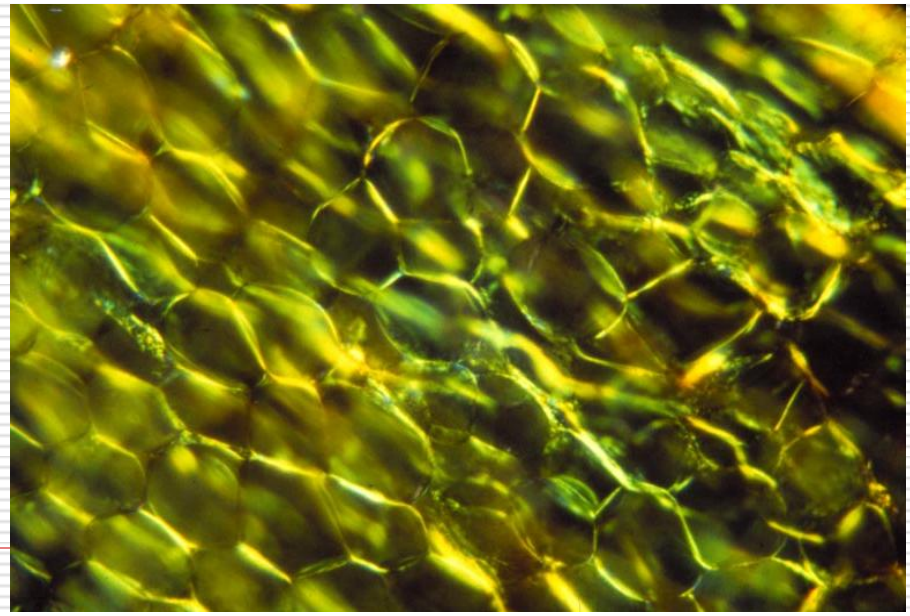
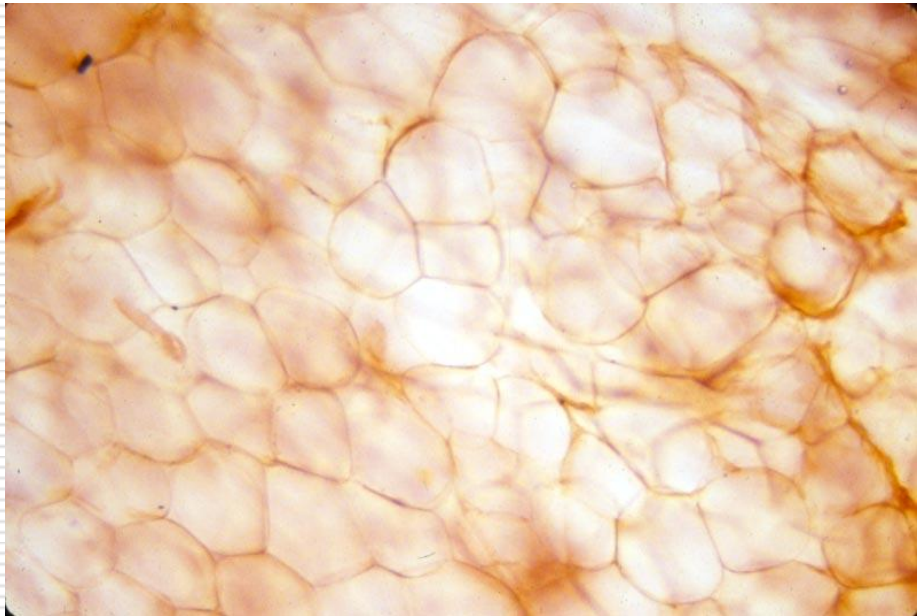
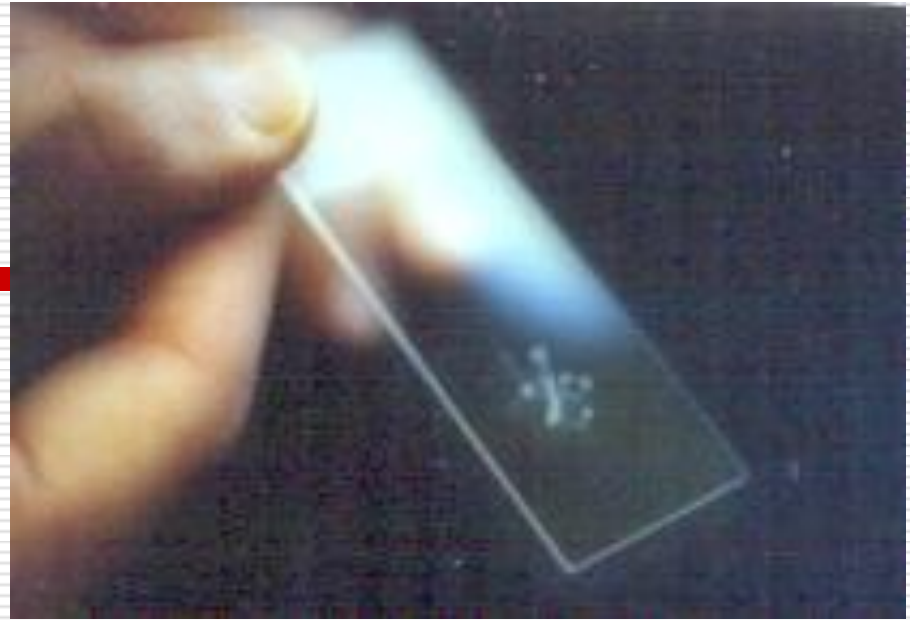
Each child has a 50-50 chance of inheriting the mutant gene

Yesterday, today, tomorrow...

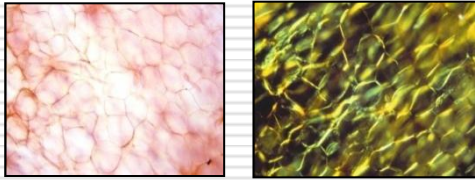
- Yesterday
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-

Making the correct diagnosis

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

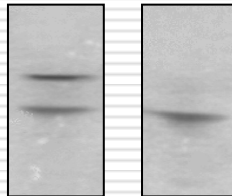


Fat or Tissue Biopsy (+)

Clinical Features

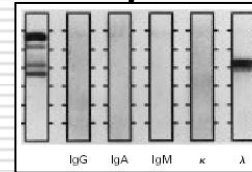
ATTR: neuropathy, cardiomyopathy, vitreous opacities
AL: proteinuria, macroglossia, neuropathy, hepatomegaly
Family History: yes or no

Isoelectric Focusing

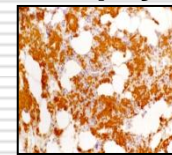


(+) (-)

Immunofixation Electrophoresis



Bone Marrow Biopsy



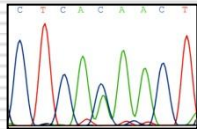
(-) **Other Amyloid Diseases**

(+) **Light Chain Amyloidosis**

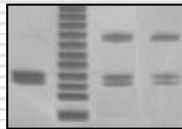
Mass spec for sequence variations and post-translational modifications

Molecular Genetics

DNA



RFLP



(-)



Other Amyloid Diseases

(+)

TTR Amyloidosis

- 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)

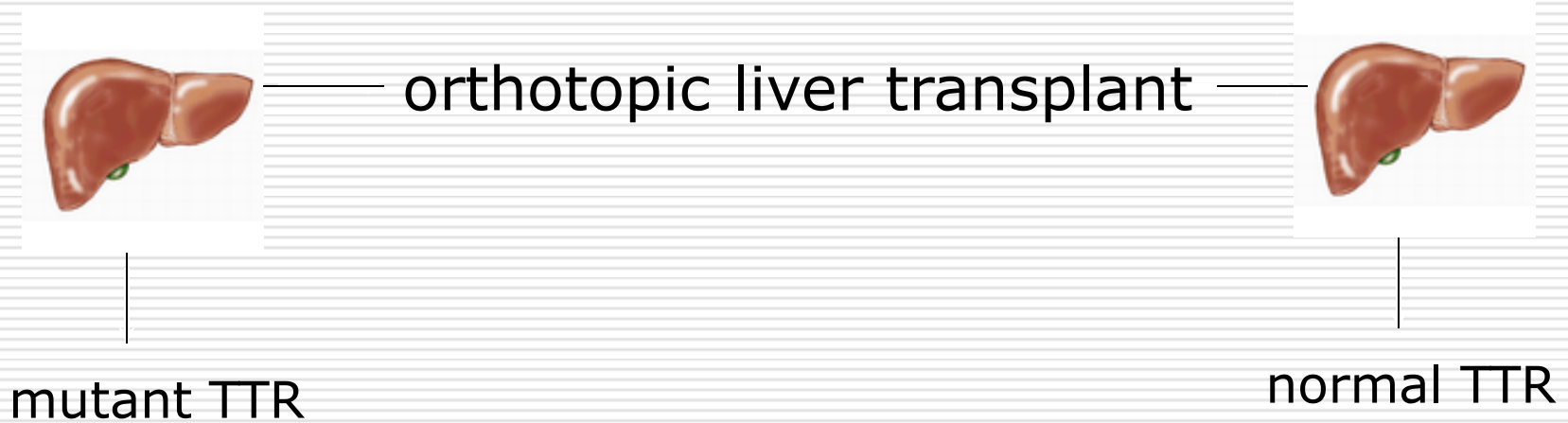
Case 1, sister

- 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



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

