Amyloid Neuropathy

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July 29, 2010
Pop Quiz: Question

- What type of amyloid is the most common cause of amyloid neuropathy?
  - ATTR
  - AA
  - AL
  - Aβ
  - Aβ2-microglobulin
Pop Quiz: Answer

- AL
Outline

- Properties of Amyloid
- Pathogenesis of Amyloidosis
- Classification & Organ System Involvement
- Amyloid Neuropathy
  - Epidemiology
  - Etiology
  - Pathogenesis
  - Clinical Findings
  - Diagnostic Evaluation
  - Treatment
  - Prognosis
- Summary
Amyloid, what is it?

A pathologic protinaceous substance, deposited in the extracellular space of various tissues and organs.
Properties of Amyloid
Physical Nature

- Continuous, nonbranching fibrils
- 7.5-10 nm diameter
- Cross-beta-pleated sheet conformation
  - ~95% fibrils
  - ~5% P component and other glycoproteins
- Identical structure in all types of amyloidosis
Types of Amyloid

- AL (amyloid light chain)
  - Ig light chains
  - Produced by plasma cells: $\lambda > \kappa$

- AA (amyloid associated)
  - Non-Ig protein derived from SAA
  - Acute phase reactant (IL-1, IL-6)
  - Synthesized in liver, choroid plexus, retinal epithelium

- A$\beta$ amyloid
  - $\beta$amyloid precursor protein (APP)
  - Chromosome 21, Alzheimer disease
Types of Amyloid, cont.

- Transthyretin (TTR)
  - Serum protein
  - Transports thyroxine and retinol
  - Mutant forms cause familial amyloid polyneuropathy or cardiomyopathy
  - Wild type form can lead to SSA, senile systemic (age-related) amyloidosis

- β2-microglobulin
  - Component of MHC class I
  - Long term hemodialysis

- Prion Proteins
  - “local amyloidosis”
  - Misfolded proteins aggregate in extracellular space
Pathogenesis
Pathogenesis

- Abnormal folding of proteins
  - Normal proteins fold improperly
  - Mutant proteins prone to misfolding

- Deposited as fibrils in extracellular tissues
  - Misfolded proteins are normally degraded
    - Intracellular: proteolysis
    - Extracellular: macrophage degradation
  - Amyloid proteins not degraded, accumulate

- Disrupt normal function
Classification

- Systemic
- Localized
- Hereditary
Systemic

- AL: 1° Amyloidosis, associated with clonal B lymphoplasmacytic diseases. All of these are AL, due to immunoglobulin light chains.
  - AL: plasma cell dyscrasia up to 30% with diagnostic features of MM
  - MM: high grade plasma cell dyscrasia with lytic bone lesions, hypercalcemia, anemia
  - WM: Waldenstrom’s macroglobulinemia (lymphoplasmacytic lymphoma) with IgM AL
  - Other B lymphomas
- AA: 2° Amyloidosis, associated with chronic inflammation, infection.
  - Rheumatoid Arthritis
  - Ankylosing Spondylitis
  - Inflammatory Bowel Disease
  - Hereditary Periodic Fever Syndromes like FMF
Localized

- Confined to a single organ
- Alzheimer’s Disease
- Prion Disease
Hereditary

- TTR
  - Familial Amyloid Polyneuropathy
- ApoAl
- Gelsolin
- Lysozyme
- Fibrinogen
Affected Organ Systems

- Kidney: proteinuria, renal failure
- Spleen: splenomegaly
- Liver: hepatomegaly, elevated alkaline phosphatase
- Heart: concentric ventricular hypertrophy, diastolic dysfunction, conduction system damage
- Endocrine: adrenal, thyroid, pituitary, pancreas
- GI: dysmotility, malabsorption, diarrhea or constipation
- Nerve: carpal tunnel syndrome, peripheral and/or autonomic neuropathy
Amyloidosis of the kidney. The glomerular architecture is almost totally obliterated by the massive accumulation of amyloid.
Liver
Cardiac Amyloidosis. A, Hematoxylin and eosin stain, showing amyloid appearing as amorphous pink material around myocytes. B, Congo red stain viewed under polarized light, in which amyloid shows characteristic apple-green birefringence (compared with collagen, which appears white).
CNS: Cerebral amyloid angiopathy

A, Massive hypertensive hemorrhage rupturing into a lateral ventricle. B, Amyloid deposition in a cortical arteriole in cerebral amyloid angiopathy; inset, Immunohistochemical staining for Aβ shows the deposited material in the vessel wall. C, Electron micrograph shows granular osmophilic material in a case of CADASIL.
Amyloid Neuropathy
History

- First described in families in Oporto, Portugal in 1952
- Andrade C. “A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves.” Brain 75 (3): 408–27
Amyloidoses and Neuropathy

- Associated with:
  - AL Amyloidosis (30%)
  - ATTR Amyloidosis: FAP familial amyloidotic polyneuropathy
  - AF Amyloidosis: Other hereditary forms
    - ApoAI
    - Gelsolin: benign cranial and sensory polyneuropathy
    - Aβ2-microglobulin: carpal tunnel syndrome

- Not associated with:
  - AA Amyloidosis
TTR-FAP: Overview

- Autosomal dominant
  - Only 1 mutant TTR allele required for disease

- Transthyretin
  - Tetrameric plasma transport protein (T4, Retinol-BP/vitA)
  - Chromosome 18
  - Synthesis in liver, choroid plexus, retinal pigment epithelium

- Mutation changes 1° protein structure
  - Variant TTR present at birth
  - Mutation destabilizes tetramer
  - Does not form amyloid until adulthood
## Table 1. Transthyretin amyloidosis.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Codon change</th>
<th>Clinical features</th>
<th>Geographic kindreds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val30Ala</td>
<td>GCG &gt; GAG</td>
<td>Heart, AN</td>
<td>USA, Italy</td>
</tr>
<tr>
<td>Val30Glu</td>
<td>GCG &gt; GAG</td>
<td>Heart, AN</td>
<td>Japan</td>
</tr>
<tr>
<td>Val30Pro</td>
<td>GCG &gt; GAG</td>
<td>Heart, AN, eye, LM</td>
<td>USA (FAP)</td>
</tr>
<tr>
<td>Pro32Gln</td>
<td>GCC &gt; GAG</td>
<td>Heart, AN, eye, LM</td>
<td>USA (FAP)</td>
</tr>
<tr>
<td>Phe33Leu</td>
<td>TTT &gt; TTA</td>
<td>Heart, AN, eye, LM</td>
<td>USA (FAP)</td>
</tr>
<tr>
<td>Cys109Gln</td>
<td>TGG &gt; TCT</td>
<td>Heart, AN, eye, LM</td>
<td>USA (FAP)</td>
</tr>
<tr>
<td>Leu12Pro</td>
<td>CTT &gt; GCT</td>
<td>Heart, AN, eye, LM</td>
<td>USA (FAP)</td>
</tr>
<tr>
<td>Leu166Pro</td>
<td>CTT &gt; GCT</td>
<td>Heart, AN, eye, LM</td>
<td>USA (FAP)</td>
</tr>
</tbody>
</table>

### Population to Population Variation

The table above illustrates the variation in clinical features and geographic kindreds associated with different mutations in the transthyretin gene. Each row represents a specific mutation, with details on the codon change, clinical features, and associated geographic kindreds. For instance, the Val30Ala mutation results in heart, AN, and is associated with kindreds in the USA and Italy. This indicates the diverse impact of these mutations across different populations, highlighting the complexity of amyloidosis genetics and its clinical manifestations.
TTR-FAP: System involvement

- PNS: most common, peripheral neuropathy
- ANS: orthostatic hypotension, alteration in GI motility
- Heart: restrictive cardiomyopathy
- Blood vessels:
  - CNS leptomeningeal amyloidosis
  - Cerebral infarcts & hemorrhage
- Renal involvement not common
TTR-FAP: Pathogenesis

A. Deposit around perforating arterioles

B. Amyloid displaces nerve fiber

C. Compression-induced demyelination and nerve fiber loss with intraneural amyloid
Arteriolar deposit
Nerve fiber displacement
Demyelination with deposits

Cross Section of Sciatic N. bundles
TTR-FAP: Location of Deposition

- Peripheral nerves
- Dorsal root ganglia
- Leptomeninges around SC and brain
- NO CNS parenchymal involvement
Clinical Progression

Sensorimotor Polyneuropathy
Slow Progression over Years

Sensory
• Small fibers
• Lower extremities
• Feet → ankles → knees
• Loss of Pain & Temp > Light Touch
• Symmetric Paresthesias
• Numbness
• Burning pain

Autonomic
• Impotence
• GI motility alterations:
  • Diarrhea
  • Constipation
• Bladder retention
• Orthostatic hypotension
• Dry mouth, dry eyes
• Vocal hoarseness (rare)

Motor
• Vocal hoarseness
• Carpal Tunnel
• Distal limb weakness
• Great toe extension
• Foot drop
Clinical Progression

Stage I
- Sensory neuropathy
- Lower limbs
- Ambulatory

Stage II
- Steppage gait
- Distal upper limbs
- Ambulatory aid

Stage III
- Bedridden
- Confined to wheelchair
- No pain or temp sensation
TTR-FAP: Other exam findings

- Neuroarthropathies (Charcot joints)

- Cranial neuropathies:
  - Progressive involvement of CN
    - V: facial sensation
    - VIII: impaired hearing
    - XII: tongue movement
  - Sparing of oculomotor nerve

- Carpal tunnel syndrome

- Blindness from vitreous opacities
ApoA1: Overview

- 12 mutations of ApoA1 gene
  - 1 mutation causes peripheral neuropathy
  - Autosomal Dominant
  - Chromosome 11
  - Gly26Arg: neuropathic variant protein

- ApoA1: Lipid metabolism
  - Apolipoprotein
  - HDL
  - Activates LCAT
    - Peripheral tissues
    - Cholesterol → Cholesterol Ester
ApoAI: System involvement

- Renal amyloid deposition, main feature
- Liver
- Spleen
- Heart
ApoAl: Pathogenesis

- **α-helical protein**
  - Variant ApoAl
  - Gly26Arg
  - Increased metabolism

- **Incomplete degradation**
  - Remodeling

- **β-pleated sheet**
  - Incorporation into amyloid fibril
  - Variant Gly26Arg only
ApoAI: Pathogenesis

Deposit around perforating arterioles

Amyloid displaces nerve fiber

Compression-induced demyelination and nerve fiber loss with intraneural amyloid
ApoAI: Location of Deposition

- Peripheral nerves
- Dorsal root ganglia
- Leptomeninges around SC and brain
- NO CNS parenchymal involvement
- Similar to TTR-FAP
Clinical Progression

Sensorimotor Polyneuropathy
Slow Progression over Years

Sensory
- Small fibers
- Lower extremities
- Feet → ankles → knees
- Loss of Pain & Temp > Light Touch
- Symmetric Paresthesias
- Numbness
- Burning pain

Autonomic
- Impotence
- GI motility alterations:
  - Diarrhea
  - Constipation
- Bladder retention

Motor
- Vocal hoarseness
- Carpal Tunnel
- Distal limb weakness
- Great toe extension
- Foot drop
- Ataxia
- Tetraparesis
ApoA1: Onset/Prognosis

- Adult onset: 30-40s
- Slowly progressive
Gelsolin: Overview

- Plasma gelsolin
  - Actin modulating protein
  - Mutations result in abnormal proteolysis
    - Asp187Asn
    - Asp187Tyr

- Systems Involved:
  - Nerve
  - Vascular
  - Renal

- Onset: ~40 years of age

- Involvement of CN VII leads to characteristic drooping of facial muscles, wrinkling, ptosis
  - Ptosis can be corrected surgically
Gelsolin: Pathogenesis

Deposit around perforating arterioles

Amyloid displaces nerve fiber

Compression-induced demyelination and nerve fiber loss with intraneural amyloid
Gelsolin: Clinical Progression

Lattice corneal dystrophy
- Age 20-30

Cranial neuropathy
- Age 40

Peripheral neuropathy
- Limb involvement
- Age >40
AL: Overview

- AL (amyloid light chain)
  - Ig light chains
  - Produced by plasma cells: \( \lambda > \kappa \)
- Sporadic
- Neuropathy:
  - 30% have associated peripheral neuropathy
  - >25% have associated carpal tunnel syndrome
- Renal involvement common (~80%)
- Cardiac involvement (~45%)
AL: Pathogenesis

A: Deposit around perforating arterioles

B: Amyloid displaces nerve fiber

C: Compression-induced demyelination and nerve fiber loss with intraneural amyloid
Clinical Progression

Sensorimotor Polyneuropathy
Slow Progression over Years

Sensory
- Small fibers
- Lower extremities
- Feet → ankles → knees
- Loss of Pain & Temp > Light Touch
- Symmetric Paresthesias
- Numbness
- Burning pain

Autonomic
- Impotence
- GI motility alterations:
  - Diarrhea
  - Constipation
- Bladder retention

Motor
- Vocal hoarseness
- Carpal Tunnel
- Distal limb weakness
- Great toe extension
- Foot drop
Diagnostic Evaluation
Diagnostic Evaluation

- Tissue biopsy to diagnose amyloid deposits
  - Fat aspirate
  - Involved organ
  - Gingival tissue or minor salivary gland
  - Sural nerve

- Amyloid Typing
  - AL
    - Bone marrow biopsy with immunohistochemistry for clonal plasma cells
    - Serum free light chain assay
    - Serum and urine immunofixation electrophoresis
  - ATTR
    - DNA sequencing
  - AA
    - Immunohistochemistry
    - Identification of underlying infection, inflammatory disease
Tissue biopsy

- Light microscopy (H&E): amorphous, eosinophilic, hyaline, extracellular substance
- Deposits induce pressure atrophy
- Peripheral nerve Wallerian Degeneration
  - Distal degeneration of axon & myelin sheath
  - Proximal axonal degeneration to next node
  - Cell body swells, nucleus is peripheralized
- Congo red stain: apple-green birefringence
Tissue Biopsy

- Nerve involvement
- Intraneural amyloid
- AL amyloidosis cannot be differentiated from TTR amyloidosis on basis of biopsy
- Immunohistochemistry with specific Abs
  - Helpful for differentiation
  - Not completely reliable
Sural Nerve Biopsy

- Vascular deposits
- No intraneural deposits seen
- Spotty nature of deposits does not exclude nerve involvement
Congo red staining

- Cross links within fibrils
- Polarized light
- Apple green birefringence
Commercial DNA Testing

- Available for TTR
  - Full TTR DNA testing if mutation unknown
  - Specific TTR sequence testing if mutation known

- Not available for:
  - ApoAl
  - Gelsolin
Treatment
Treatment Goals

<table>
<thead>
<tr>
<th>Principle</th>
<th>Target</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Destruction or removal</td>
<td>Precursor cells</td>
<td>Liver transplantation (TTR-NAF)</td>
</tr>
<tr>
<td>Removal</td>
<td></td>
<td>[1;27]</td>
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<tr>
<td>Inhibition of TTR fibril</td>
<td>Soluble protein</td>
<td>Chemotherapy (AL neuropathy)</td>
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<tr>
<td>formation</td>
<td>precursor</td>
<td>[15;45]</td>
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<tr>
<td>Resorption</td>
<td>Amyloid deposit</td>
<td>Ribozymes (TTR-FAP)</td>
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<tr>
<td></td>
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<td>Plasma Exchanges</td>
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<td></td>
<td></td>
<td>NSAI drugs (TTR-FAP)</td>
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<tr>
<td></td>
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<td>[30]*</td>
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</table>
Treatment

- Nonspecific
- Specific
Nonspecific Treatment

- Treat painful neuropathic symptoms

- Agents:
  - Gabapentin
  - Amitryptyline
  - Pregabalin
  - Duloxetine
  - Tricyclic antidepressants, may exacerbate orthostasis
  - Opioid analgesics

- Response to drug may change as disease progresses
Specific Treatment: TTR-FAP

- Orthotopic liver transplantation
  - Remove mutant TTR, synthesized in liver
  - Val30Met mutation best prognosis: 80% 5 year survival
  - Other mutations: 55-60% 5 year survival
  - Some evidence of efficacy for ApoAI

- Vitrectomy for corneal amyloid deposits

- Small molecules to stabilize the normal TTR tetramer
  - Diflunisal (NSAID)
  - Tafamidis
Specific Treatment: Gelsolin

- Lattice corneal dystrophy
  - Method: Corneal transplantation

- Cutis laxis & blepharochalasis (resultant from facial palsy)
  - Method: Plastic surgery

- Note: Gelsolin is essential protein of actin function
  - Rx aimed to eliminate production will likely not be tolerated
Specific Treatment: AL

- Anti-plasma cell chemotherapy
  - Oral melphalan chemotherapy (relatively ineffective)
  - High dose IV melphalan and autologous stem cell transplantation
- New agents
  - Bortezomib, proteasome inhibitor
  - Lenalidomide, immunomodulator
  - Others
Summary
## Summary: Overview

<table>
<thead>
<tr>
<th></th>
<th>TTR-FAP</th>
<th>ApoA1</th>
<th>AL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Onset</strong></td>
<td>30s-70s</td>
<td>30s-40s</td>
<td>Usually older pts</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>M&gt;F</td>
<td>M=F</td>
<td>M&gt;F</td>
</tr>
<tr>
<td><strong>Associated Systems</strong></td>
<td>Sensorimotor</td>
<td>Sensorimotor</td>
<td>Sensorimotor</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>Weight loss</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>Heart Failure</td>
<td>Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td>Renal Failure</td>
<td>Renal Failure</td>
</tr>
<tr>
<td></td>
<td>Corneal Dystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family History</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cause of Death</strong></td>
<td>Heart failure,</td>
<td>Renal failure</td>
<td>Heart failure,</td>
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<tr>
<td></td>
<td>wasting syndrome</td>
<td></td>
<td>arrhythmia,</td>
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<td></td>
<td></td>
<td></td>
<td>bleeding</td>
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## Summary: Clinical Findings

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Context</th>
</tr>
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<tbody>
<tr>
<td>1. Progressive distal symmetrical sensory polyneuropathy</td>
<td>A. Absence of diabetes</td>
</tr>
<tr>
<td>Predominantly pain and thermal sensory loss (+ ++ +)</td>
<td>B. Positive family story of FAP</td>
</tr>
<tr>
<td>2. Progressive distal symmetrical sensorymotor polyneuropathy</td>
<td>C. Monoclonal gammopathy (benign or malignant)</td>
</tr>
<tr>
<td>3. Autonomic dysfunction</td>
<td>Electrophysiological study</td>
</tr>
<tr>
<td>4. Other manifestations: Neuritis multiplex, Carpal tunnel syndrome, Cranial neuropathy, ...</td>
<td>D. Axonal pattern</td>
</tr>
</tbody>
</table>

### Situations suggestive of amyloid neuropathy
- (1+3) & A
- (1 or 2 or 3) & B
- (1 or 2) & D & unknown origin
- (1 + 3) & (C + D)
- (2 + 3) & (C + D)
- 4
Summary: Diagnosis & Treatment

Patient with suspicion of amyloid polyneuropathy

Positive family story
- Yes
- No

Genetic study
- Positive
- Negative

Nerve Biopsy
- Amyloid Deposits?

Immunoelectrophoresis
- Monoclonal Protein
  - Absent
  - Present

Light chain (AL)
- Amyloid Neuropathy

FAP

Liver transplantation?

Genetic Counselling
- Prenatal diagnosis
- Presymptomatic diagnosis

Genetic Counselling

Chemotherapy
- Intensive?
Take Home Points

- Amyloidosis should not be considered a single disease
- All amyloid has a similar structure of β-sheet fibrils
- Amyloid is either misfolded normal protein or mutant protein. Both deposit extracellularly and disrupt adjacent normal tissue function
- Neuropathy occurs with AL and AF, particularly ATTR
- Biopsy is required for diagnosis of systemic amyloidosis, following by genetic, hematologic, immunochemical, and proteomics for typing
- Treatment methods are both nonspecific and specific
Thank you
References & Images


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