Amyloid Neuropathy

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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

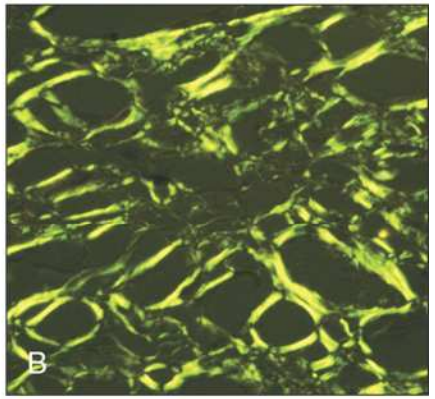
Amyloid, what is it?

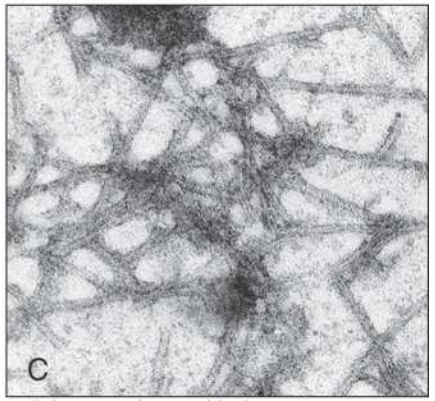
A pathologic protinaceous substance, deposited in the extracellular space of various tissues and organs.

Properties of Amyloid

Physical Nature

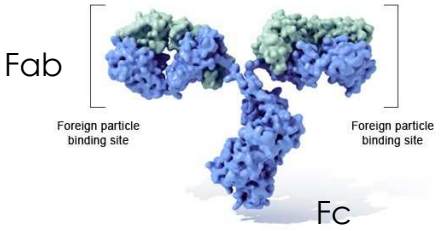
- Continuous, nonbranching fibrils
- 7.5-10 nm diameter
- Cross-beta-pleated sheet conformation
  - ~95% fibrils
  - ~5% P component and other glycoproteins
- Identical structure in all types of amyloidosis

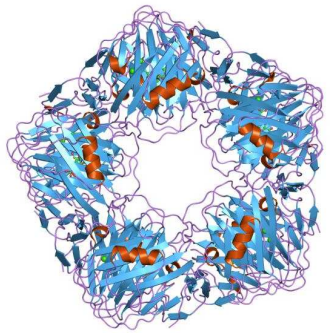




Types of Amyloid

- AL (amyloid light chain)
  - Ig light chains
  - Produced by plasma cells: λ > κ
- AA (amyloid associated)
  - Non-Ig protein derived from SAA
  - Acute phase reactant (IL-1, IL-6)
  - Synthesized in liver, choroid plexus, retinal epithelium
- Aβ amyloid
  - βamyloid precursor protein (APP)
  - Chromosome 21, Alzheimer disease





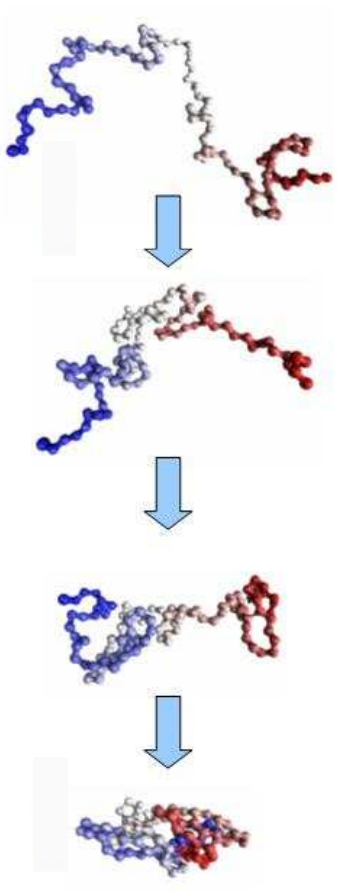
Types of Amyloid, cont.

- 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

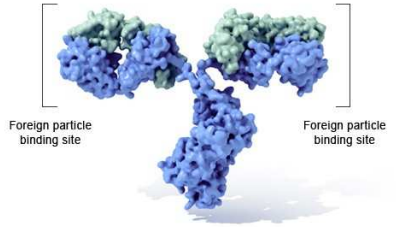
Systemic

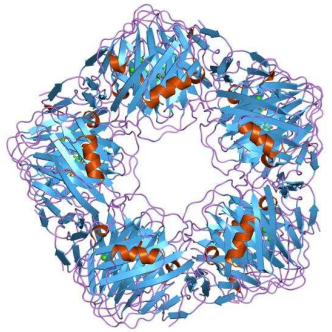
Localized

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

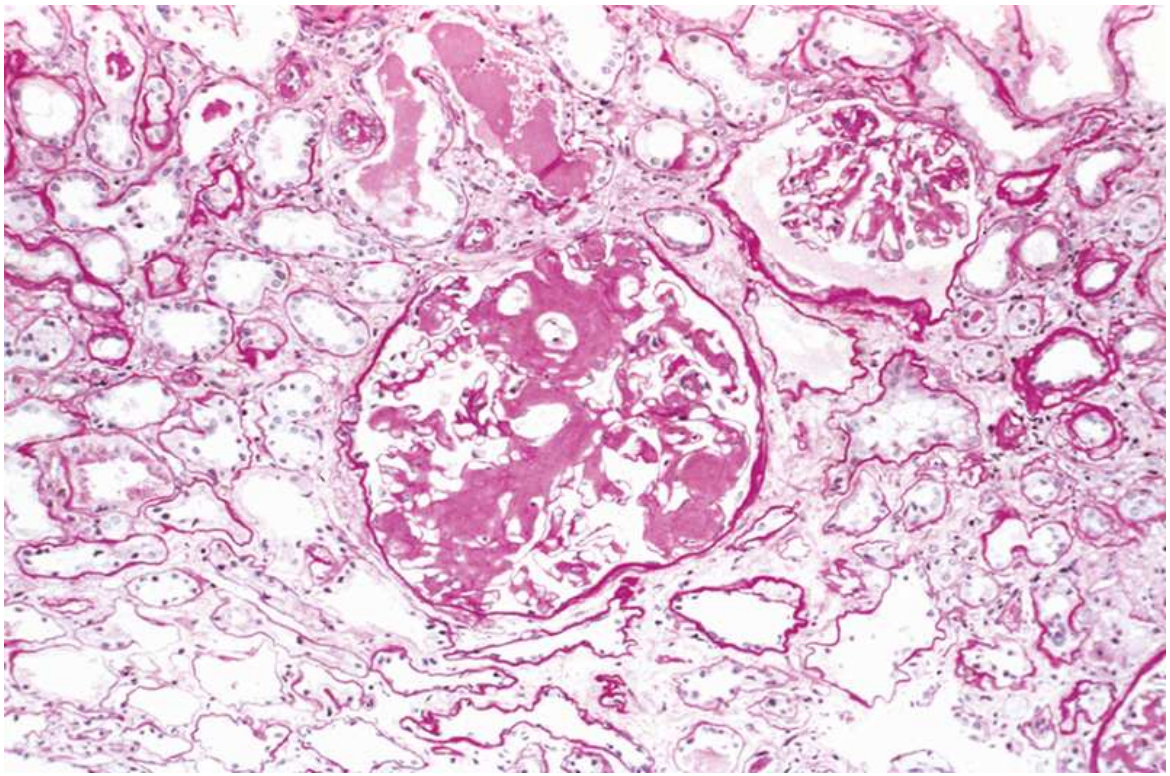
Hereditary

- TTR
  - Familial Amyloid Polyneuropathy
- ApoAI
- Gelsolin
- Lysozyme
- Fibrinogen

Affected Organ Systems

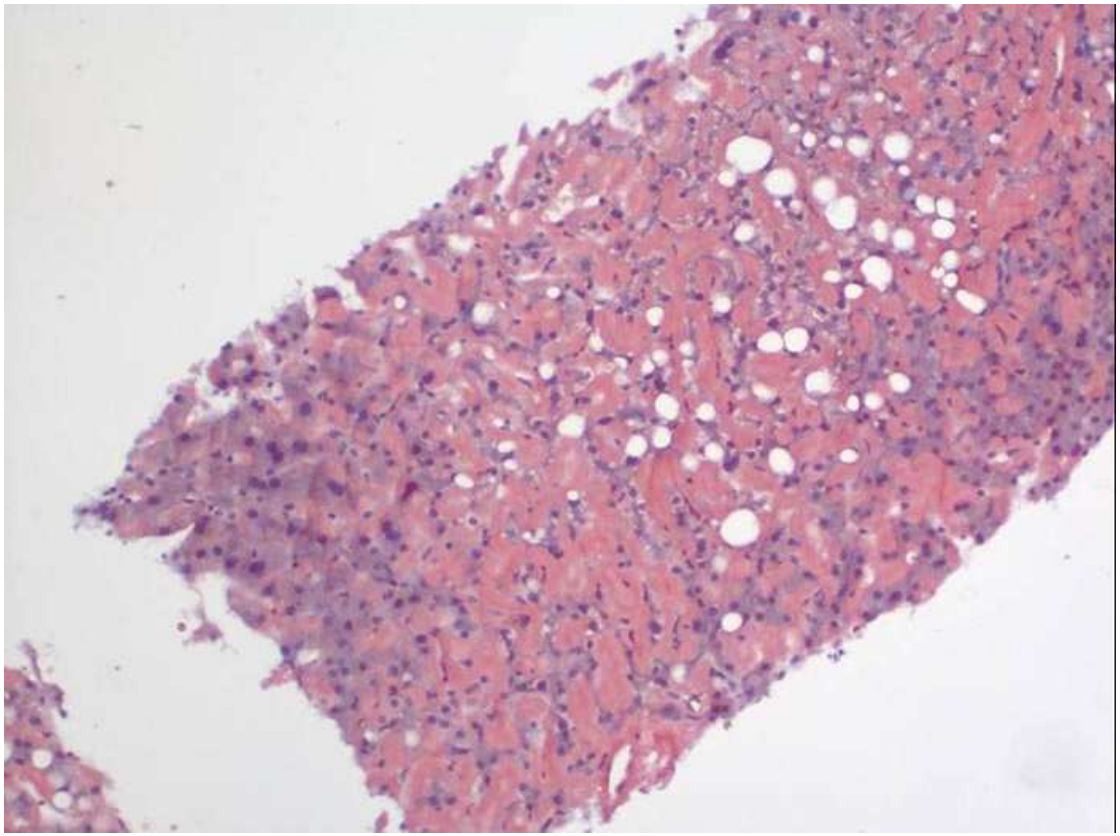
- Kidney: proteinuria, renal failure
- Spleen: splenomegaly
- Liver: hepatomegaly, elevated alkaline phosphatase
- Heart: concentric ventricular hypertrophy, diastolic dysfunction, conduction system damage
- Endocrine: adrenal, thyroid, pituitary, pancreas
- GI: dysmotility, malabsorption, diarrhea or constipation
- Nerve: carpal tunnel syndrome, peripheral and/or autonomic neuropathy

Kidney

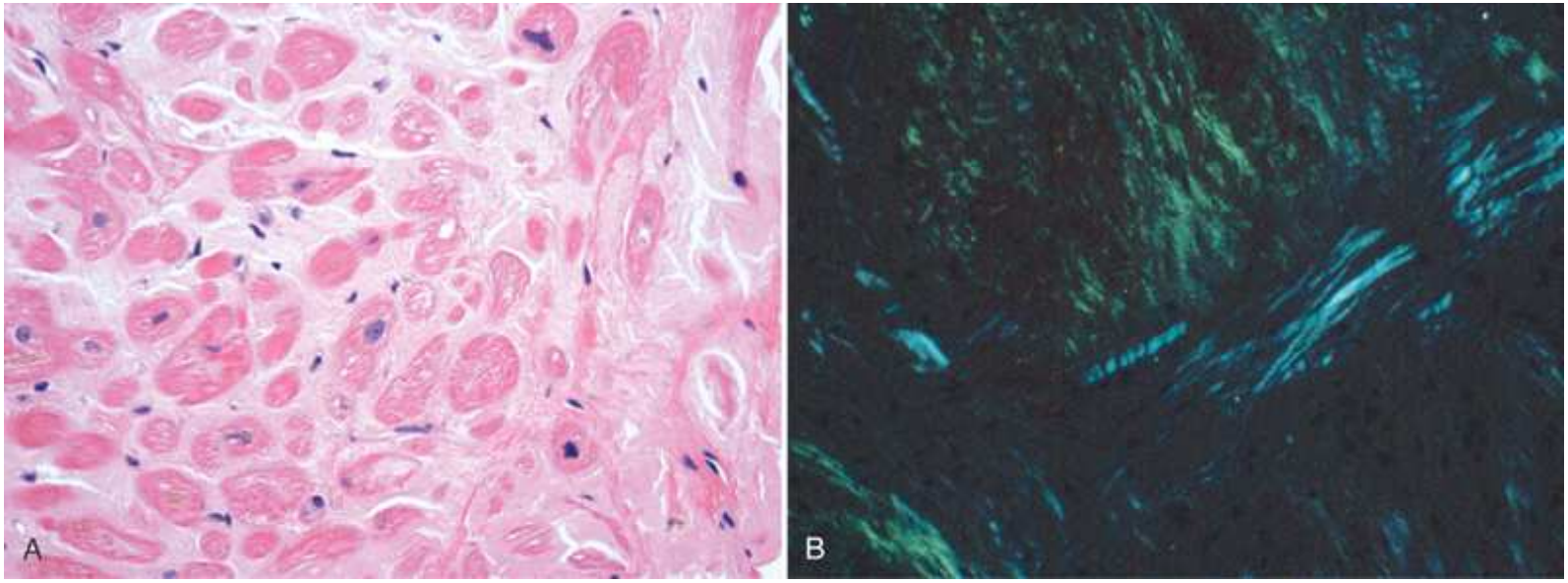


Amyloidosis of the kidney. The glomerular architecture is almost totally obliterated by the massive accumulation of amyloid.

Liver

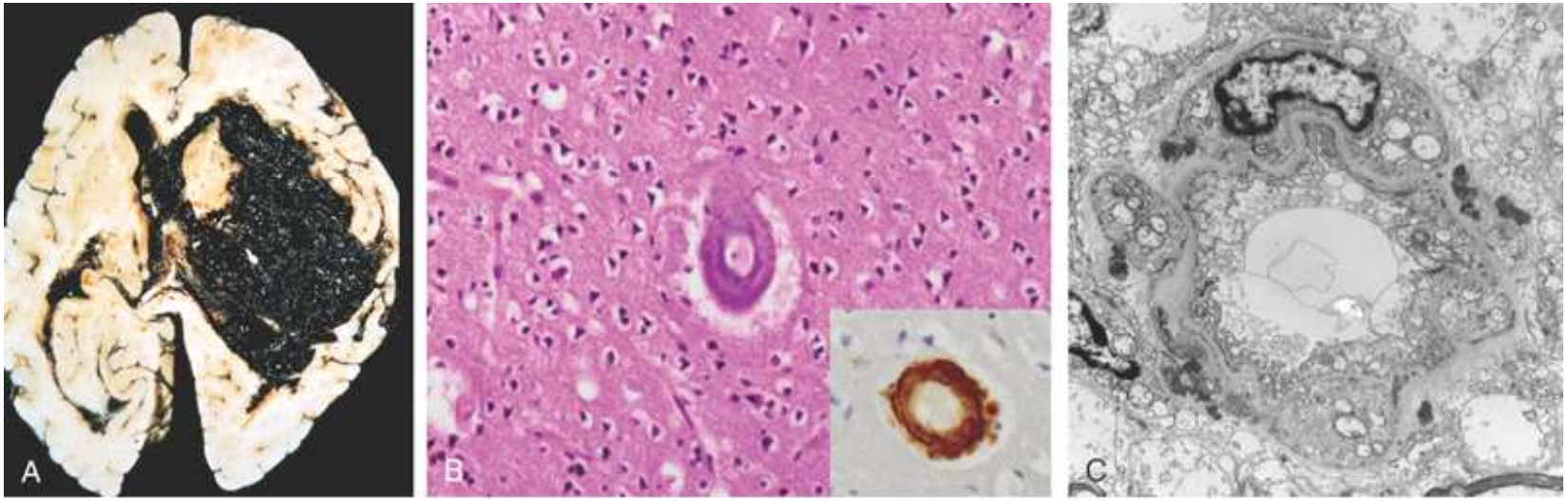


Heart



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

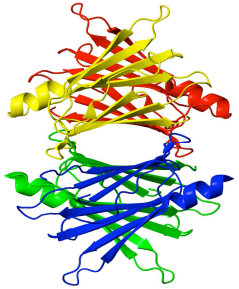
History

- 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

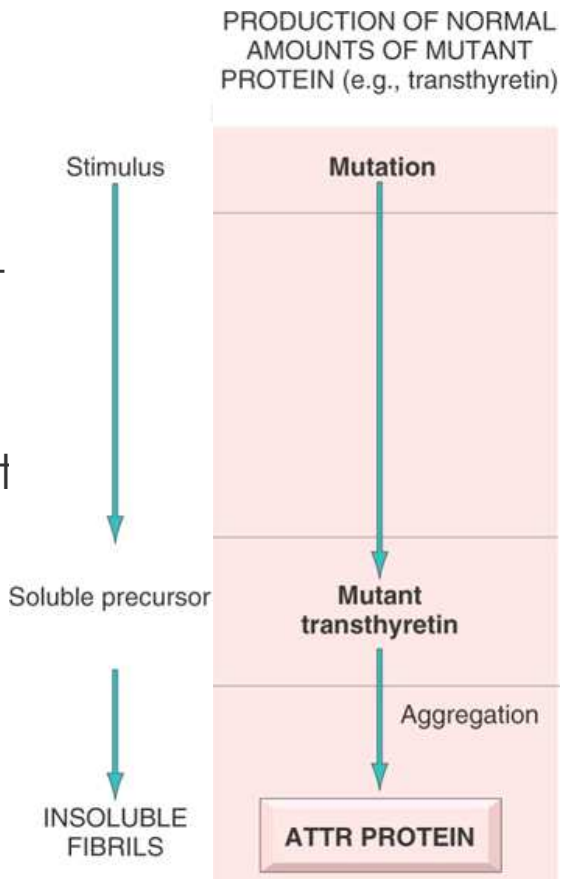
Amyloidoses and Neuropathy

- 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 (T_4, 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



TTR-FAP: >100 mutations

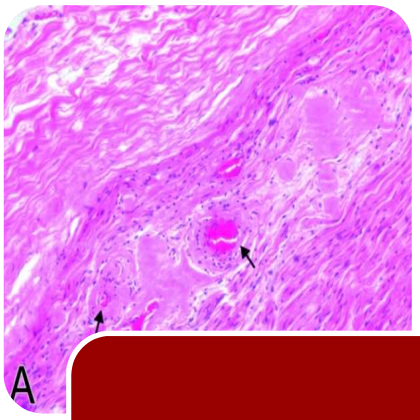
Table 1. Transthyretin amyloidosis.

Mutation	Codon change	Clinical features*	Geographic kindreds	Mutation	Codon change	Clinical features*	Geographic kindreds
Cys10Arg	TGT–CGT	Heart, eye, PN	USA (PA)	Leu55Pro	CTG–CCG	Heart, AN, eye	USA, Taiwan
Leu12Pro	CTG–CCG	LM	UK	Leu55Arg	–CGG	LM	Germany
Asp18Glu	GAT–GAA	PN	South America, USA	Leu55Gln	–CAG	Eye, PN	USA
Asp18Gly	–GGT	LM	Hungary	Leu55Glu	CTG–CAG	Heart, PN, AN	Sweden
Asp18Asn	–AAT	Heart	USA	His56Arg	CAT–CGT	Heart	USA
Val20Ile	GTC–ATC	Heart, CTS	Germany, USA	Gly57Arg	GGG–AGG	Heart	Sweden
Ser23Asn	AGT–AAT	Heart, PN, eye	USA	Leu58His	CTC–CAC	CTS, heart	USA (MD) (FAP II)
Pro24Ser	CCT–TCT	Heart, CTS, PN	USA	Leu58Arg	–CGC	CTS, AN, eye	Japan
Ala25Ser	GCC–TCC	Heart, CTS, PN	USA	Thr59Lys	ACA–AAA	Heart, PN, AN	Italy, USA (Chinese)
Ala25Thr	–ACC	LM, PN	Japan	Thr60Ala	ACT–GCT	Heart, CTS	USA (Appalachian)
Val28Met	GTG–ATG	PN, AN	Portugal	Glu61Lys	GAG–AAG	PN	Japan
Val30Met	GTG–ATG	PN, AN, eye, LM	Portugal, Japan, Sweden, USA (FAP I)	Glu61Gly	–GGG	Heart, PN	USA
Val30Ala	–GCG	Heart, AN	USA	Phe64Leu	TTT–CTT/TTG	PN, CTS, heart	USA, Italy
Val30Leu	–CTG	PN, heart	Japan	Phe64Ser	–TCT	LM, PN, eye	Canada, UK
Val30Gly	–GGG	LM, eye	USA	Ile68Leu	ATA–TTA	Heart	Germany
Val32Ala	GTG–GCG	PN	Israel	Tyr69His	TAC–CAC	Eye, LM	Canada, USA
Phe33Ile	TTC–ATC	PN, eye	Israel	Tyr69Ile	–ATC†	Heart, CTS, AN	Japan
Phe33Leu	–CTC	PN, heart	USA	Lys70Asn	AAA–AAC	Eye, CTS, PN	USA
Phe33Val	–GTC	PN	UK, Japan, China	Val71Ala	GTG–GCG	PN, Eye, CTS	France, Spain
Phe33Cys	–TGC	CTS, heart, eye, kidney	USA	Ile73Val	ATA–GTA	PN, AN	Bangladesh
Arg34Thr	AGA–ACA	PN, heart	Italy	Ser77Tyr	TCT–TAT	Kidney	USA (IL, TX), France
Arg34Gly	AGA–GGA	Eye	UK	Ser77Phe	–TTT	PN, AN, heart	France
Lys35Asn	AAG–AAC	PN, AN, heart	France	Tyr78Phe	TAC–TTC	PN, CTS, skin	France
Lys35Thr	–ACG	Eye	USA	Ala81Thr	GCA–ACA	Heart	USA
Ala36Pro	GCT–CCT	Eye, CTS	USA	Ala81Val	GCA–GTA	Heart	UK
Asp38Ala	GAT–GCT	PN, heart	Japan	Ile84Ser	ATC–AGC	Heart, CTS, eye	USA (IN), Hungary (FAP II)
Trp41Leu	TGG–TTG	Eye, PN	USA	Ile84Asn	–AAC	Heart, eye	USA
Glu42Gly	GAG–GGG	PN, AN, heart	Japan, USA, Russia	Ile84Thr	–ACC	Heart, PN	Germany, UK
Glu42Asp	–GAT	Heart	France	His88Arg	CAT–CGT	Heart	Sweden
Phe44Ser	TTT–TCT	PN, AN, heart	USA	Glu89Gln	GAG–CAG	PN, heart	Italy
Ala45Thr	GCC–ACC	Heart	USA	Glu89Lys	–AAG	PN, heart	USA
Ala45Asp	–GAC	Heart, PN	USA	His90Asp	CAT–GAT	Heart	UK
Ala45Ser	–TCC	Heart	Sweden	Ala91Ser	GCA–TCA	PN, CTS, heart	France
Gly47Arg	GGG–CGG/AGG	PN, AN	Japan	Glu92Lys	GAG–AAG	Heart	Japan
Gly47Ala	–GCG	Heart, AN	Italy, France	Val94Ala	GTA–GCA	Heart, PN, AN, kidney	Germany, USA
Gly47Val	–GTG	CTS, PN, AN, heart	Sri Lanka	Ala97Gly	GCC–GGC	Heart, PN	Japan
Gly47Glu	–GAG	Heart, PN, AN	Turkey, USA, Germany	Ala97Ser	–TCC	PN, heart	Taiwan, USA
Thr49Ala	ACC–GCC	Heart, CTS	France, Italy	Ile107Val	ATT–GTT	Heart, CTS, PN	USA
Thr49Ile	–ATC	PN, heart	Japan, Spain	Ile107Met	–ATG	PN, heart	Germany
Thr49Pro	–CCC	Heart, PN	USA	Ile107Phe	ATT–TTT	PN, AN	UK
Ser50Arg	AGT–AGG	AN, PN	Japan, France/Italy, USA	Ala109Ser	GCC–TCC	PN, AN	Japan
Ser50Ile	–ATT	Heart, PN, AN	Japan	Leu111Met	CTG–ATG	Heart	Denmark
Glu51Gly	GAG–GGG	Heart	USA	Ser112Ile	AGC–ATC	PN, heart	Italy
Ser52Pro	TCT–CCT	PN, AN, Heart, kidney	UK	Tyr114Cys	TAC–TGC	PN, AN, eye, LM	Japan, USA

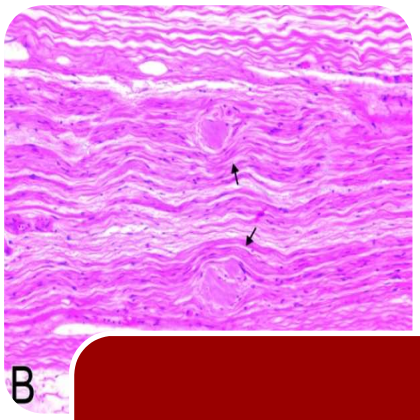
TTR-FAP: System involvement

- 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

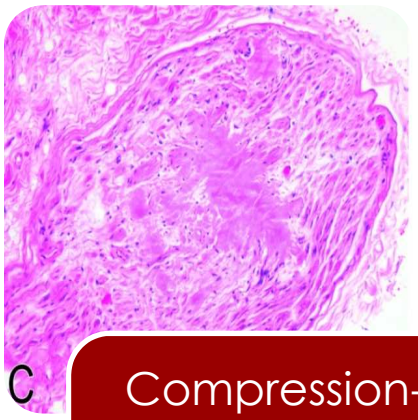
TTR-FAP: Pathogenesis



Deposit around perforating arterioles

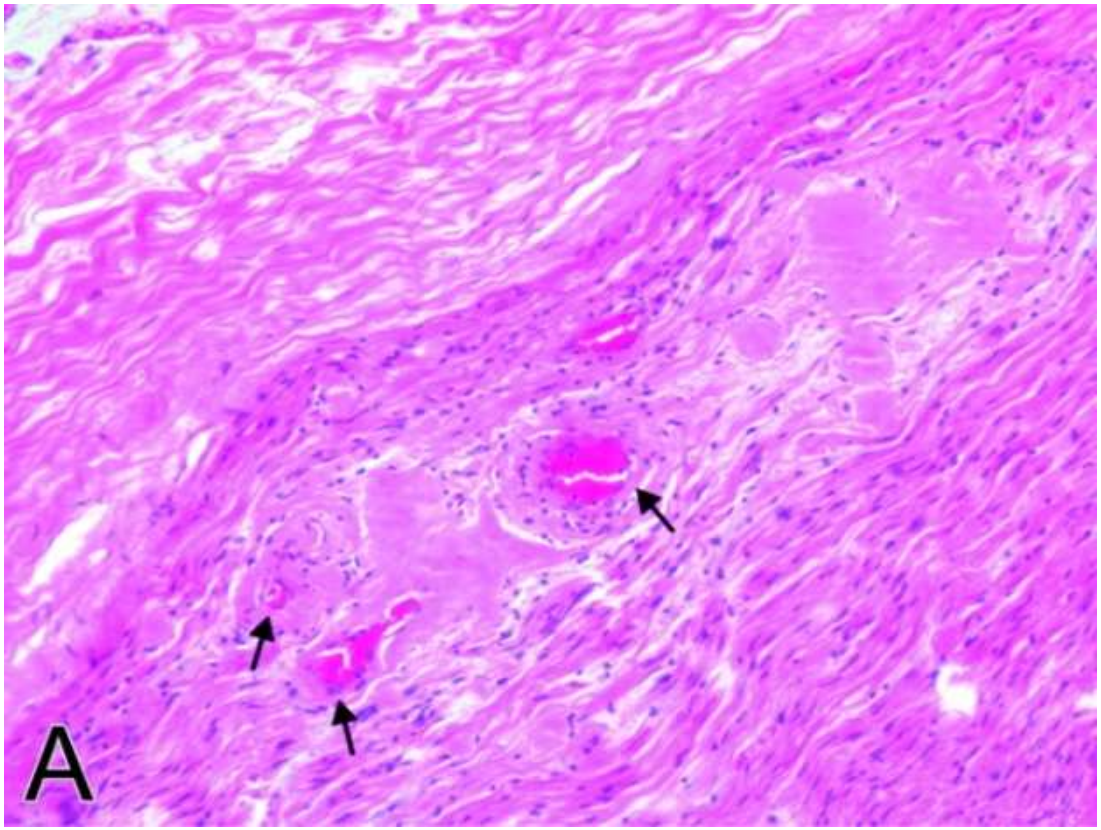


Amyloid displaces nerve fiber

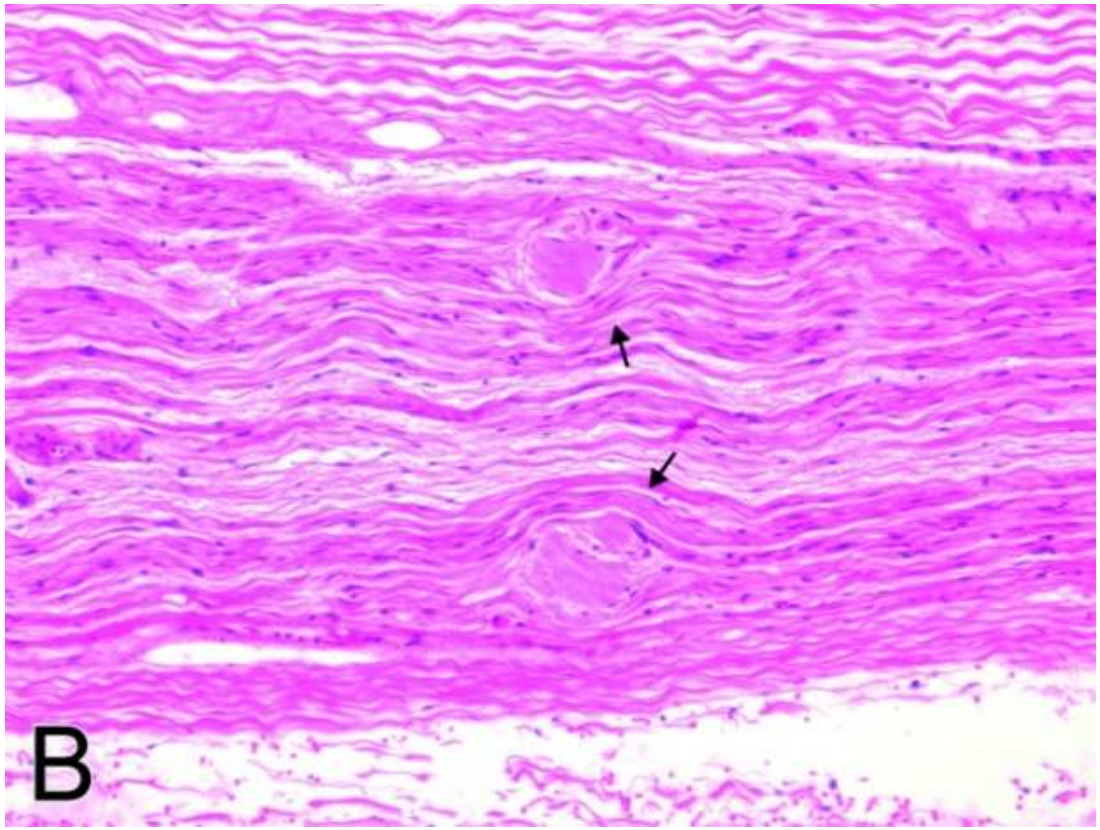


Compression-induced demyelination and nerve fiber loss with intraneural amyloid

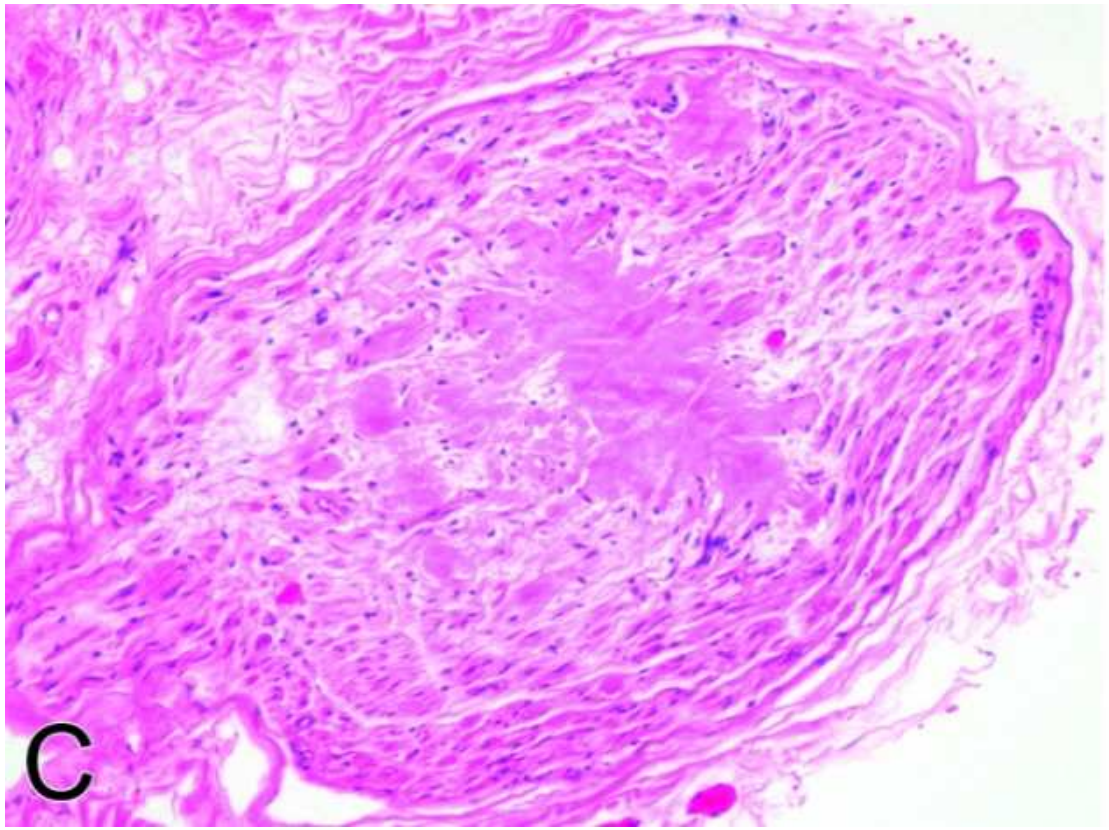
Arteriolar deposit



Nerve fiber displacement



Demyelination with deposits



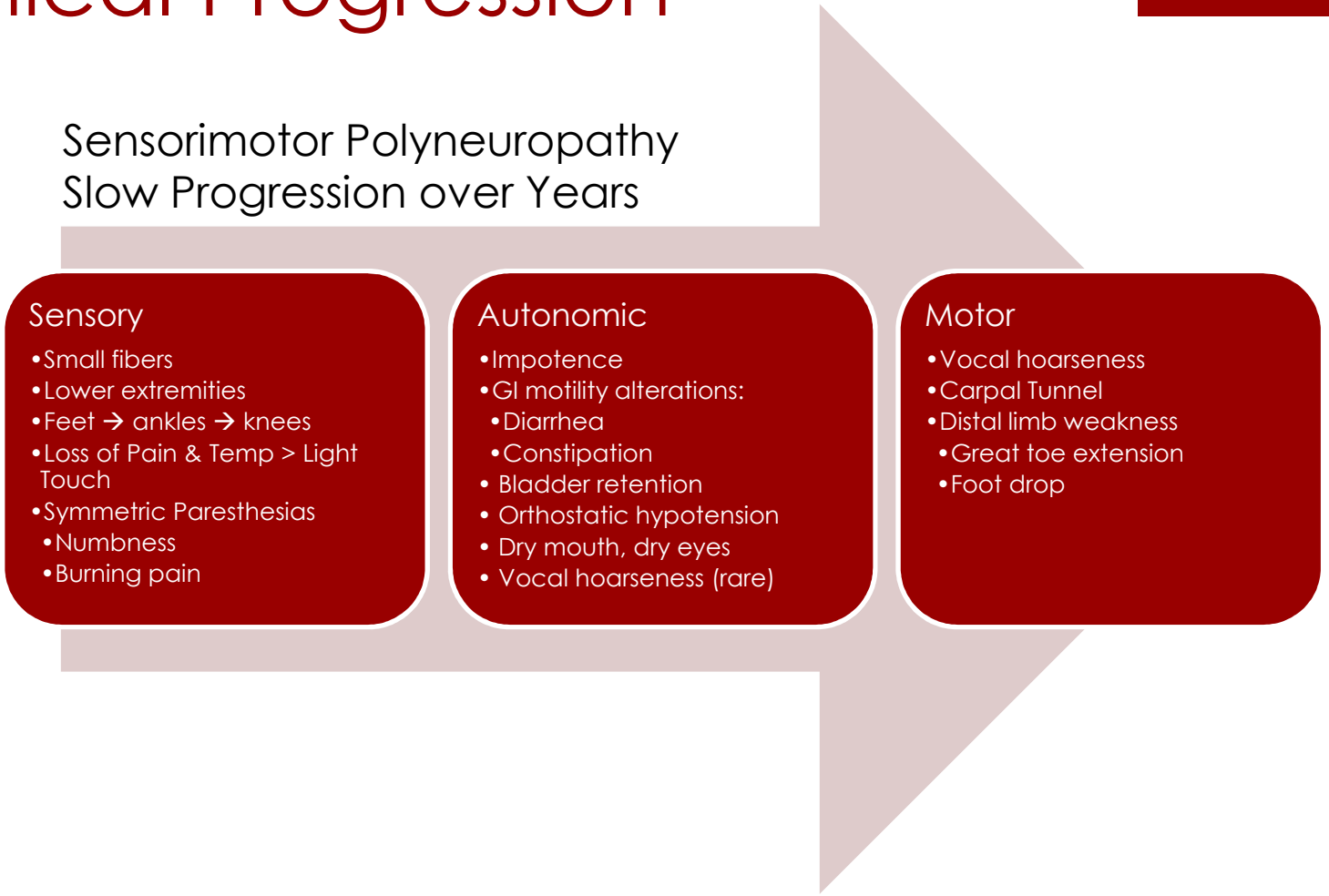
Cross Section of Sciatic N. bundles

TTR-FAP: Location of Deposition

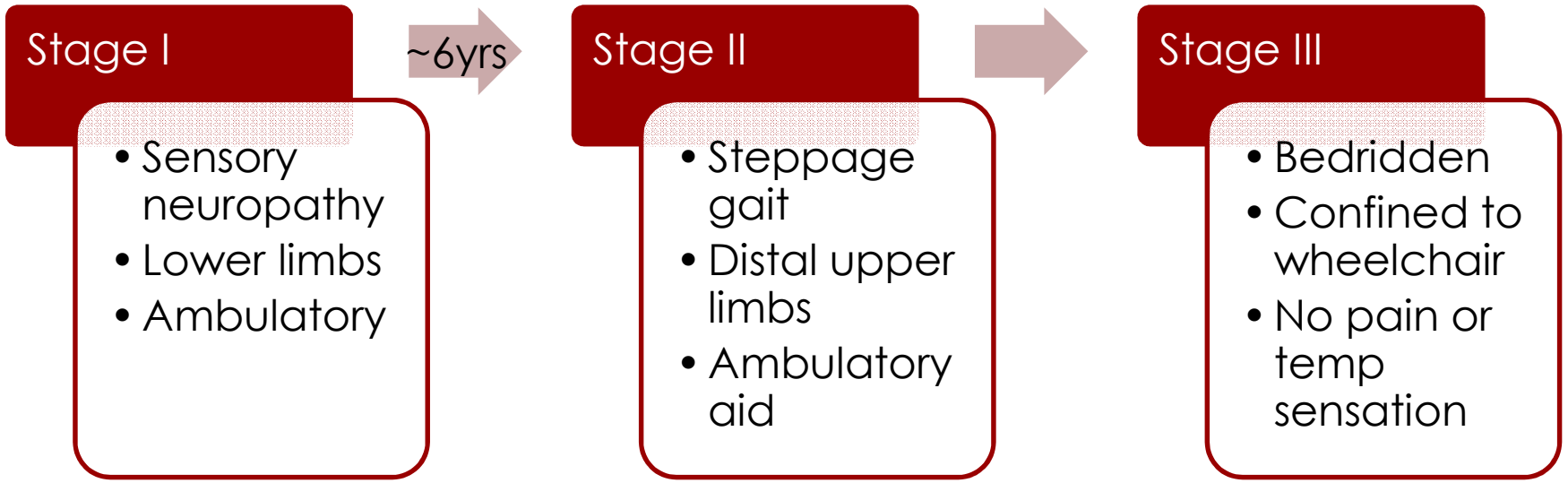
- Peripheral nerves
- Dorsal root ganglia
- Leptomeninges around SC and brain
- NO CNS parenchymal involvement

Clinical Progression

Sensorimotor Polyneuropathy
Slow Progression over Years



Clinical Progression

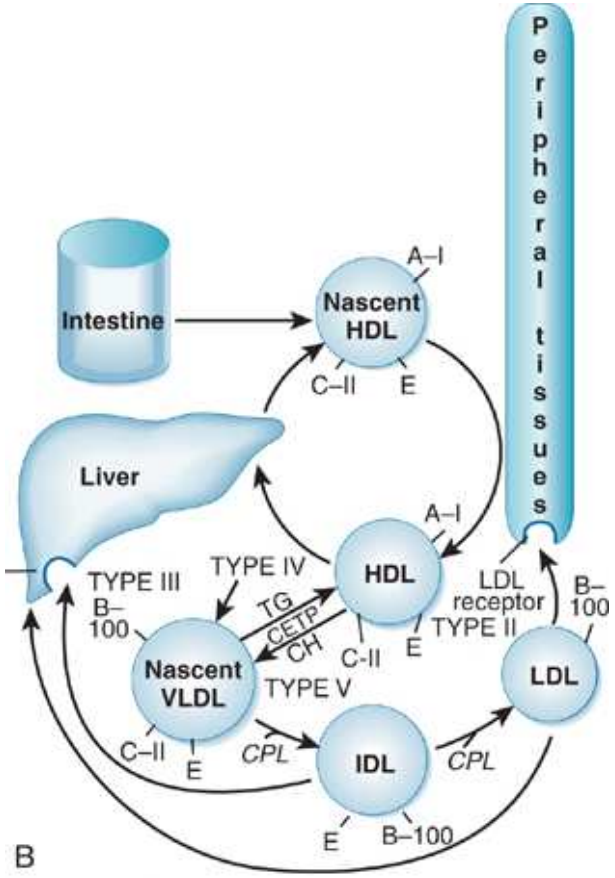


TTR-FAP: Other exam findings

- 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

ApoAI: Overview

- 12 mutations of ApoAI 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

ApoAI: Pathogenesis

α-helical protein

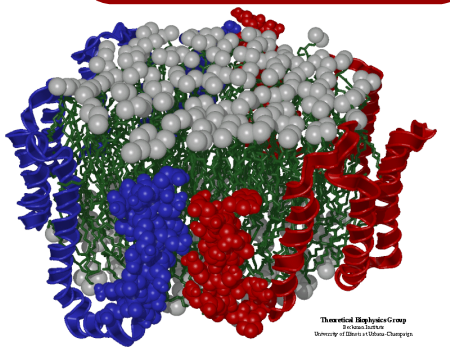
- Variant ApoAI
- Gly26Arg
- Increased metabolism

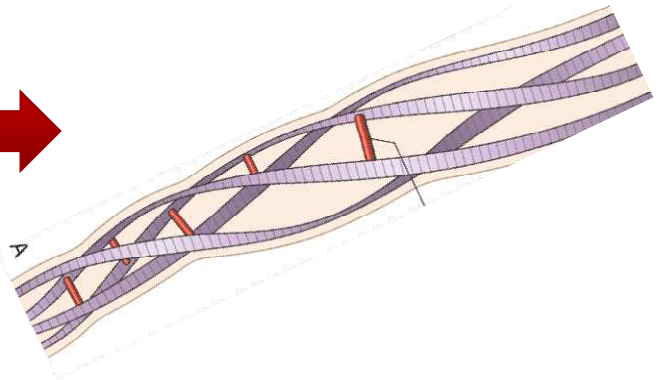
Incomplete degradation

- Remodeling

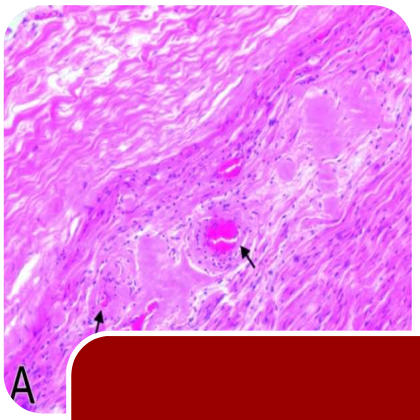
β-pleated sheet

- Incorporation into amyloid fibril
- Variant Gly26Arg only

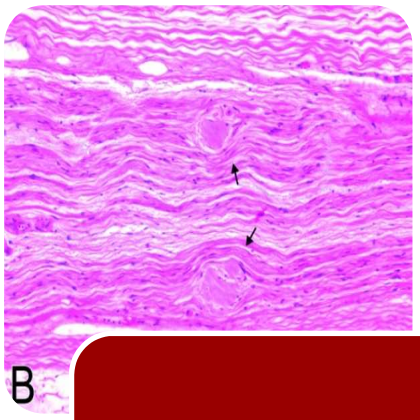




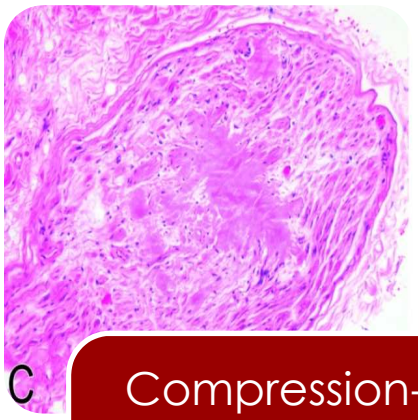
ApoAI: Pathogenesis



Deposit around perforating arterioles



Amyloid displaces nerve fiber



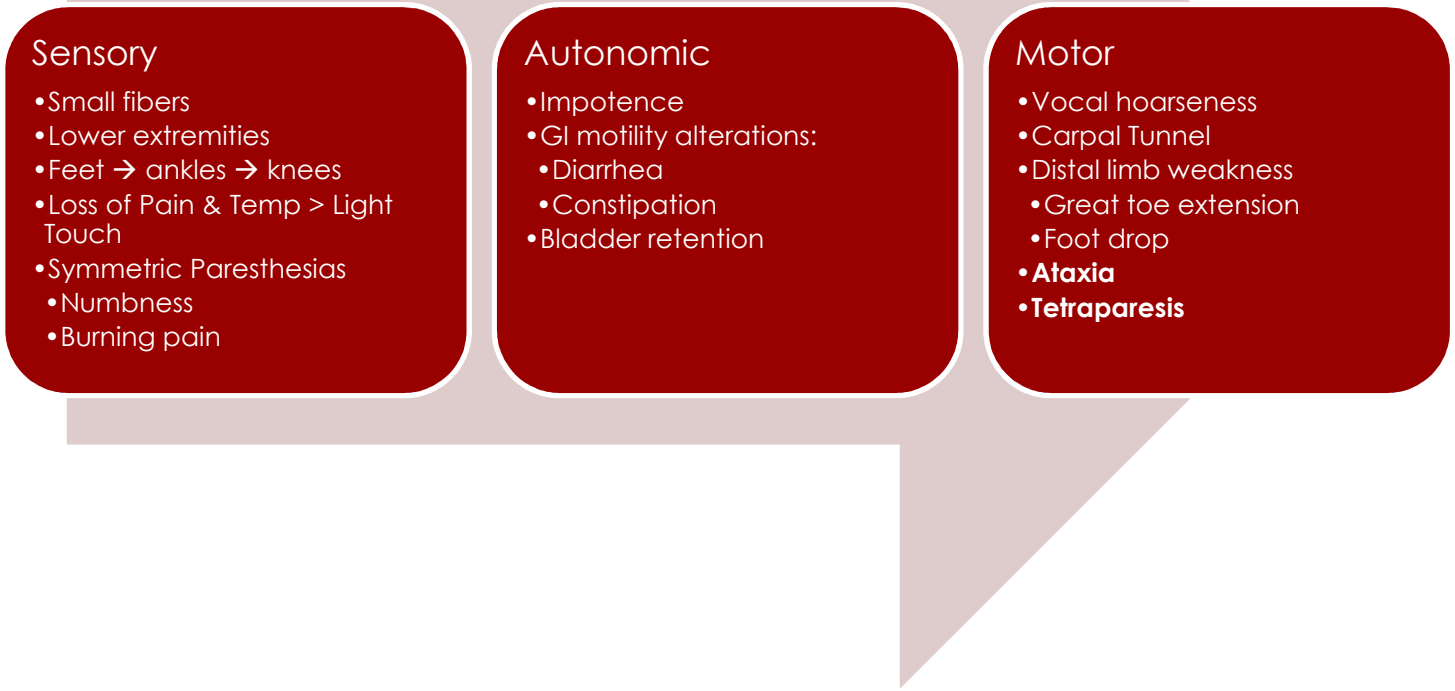
Compression-induced demyelination and nerve fiber loss with intraneural amyloid

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



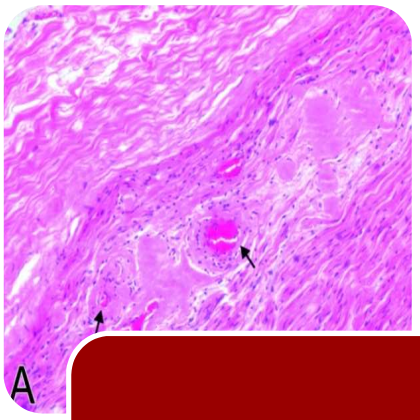
ApoA1: Onset/Prognosis

- 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



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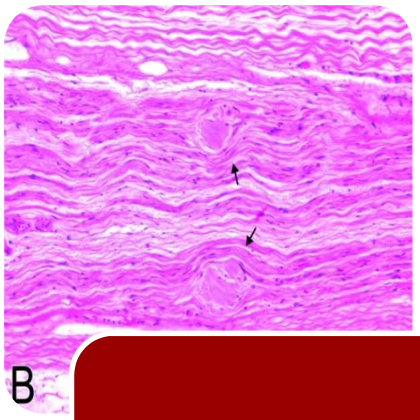

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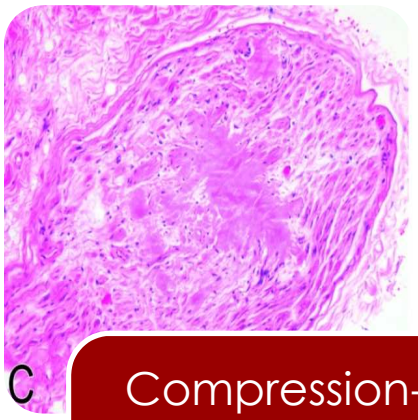


Compression-induced demyelination and nerve fiber loss with intraneural amyloid

Gelsolin: Clinical Progression

Lattice corneal dystrophy

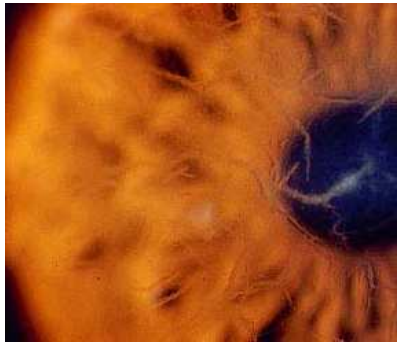
- Age 20-30

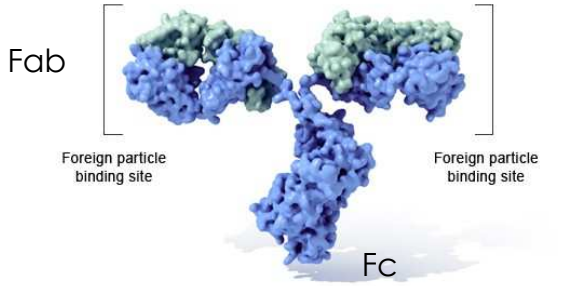
Cranial neuropathy

- Age 40

Peripheral neuropathy

- Limb involvement
- Age >40

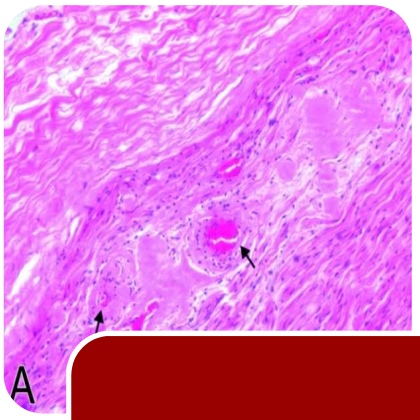




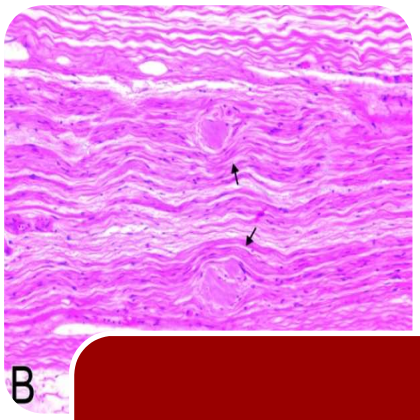
AL: Overview

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

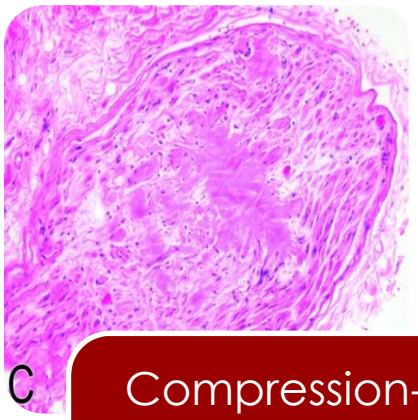
AL: Pathogenesis



Deposit around perforating arterioles



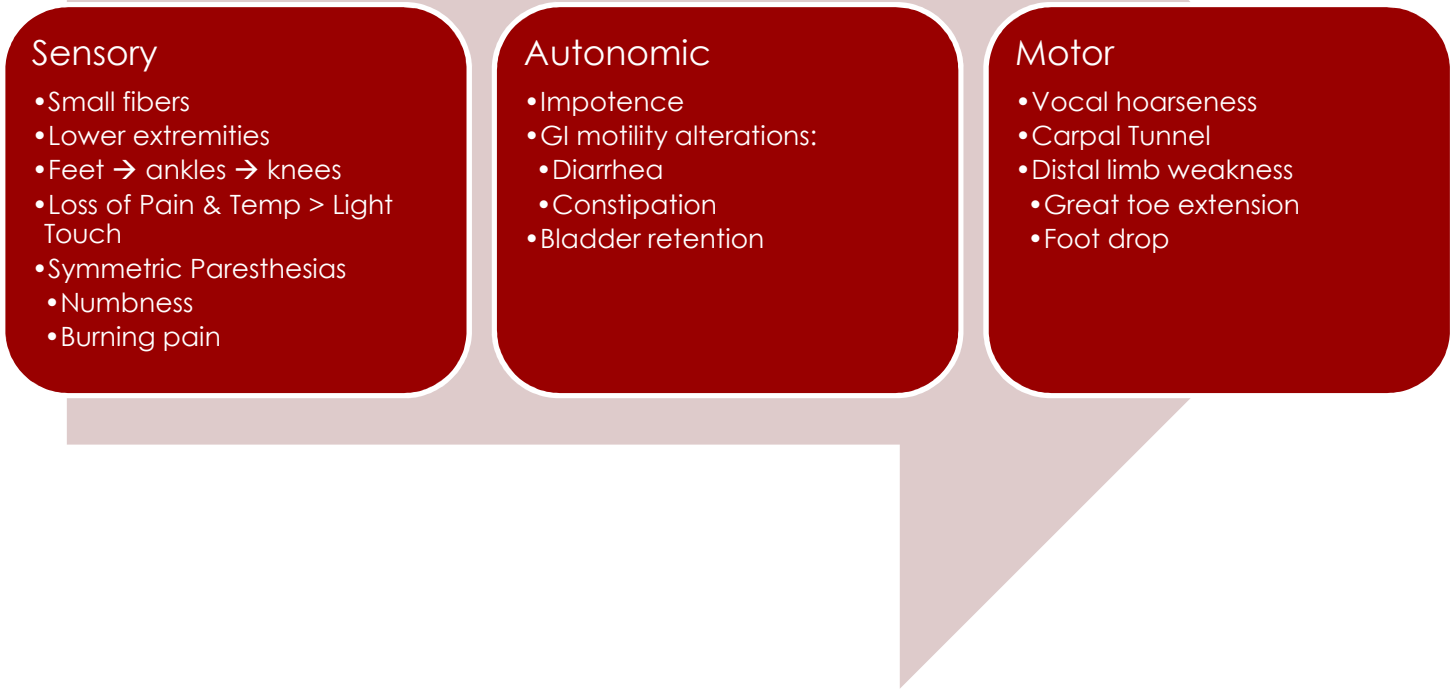
Amyloid displaces nerve fiber



Compression-induced demyelination and nerve fiber loss with intraneural amyloid

Clinical Progression

Sensorimotor Polyneuropathy
Slow Progression over Years



Diagnostic Evaluation

Diagnostic Evaluation

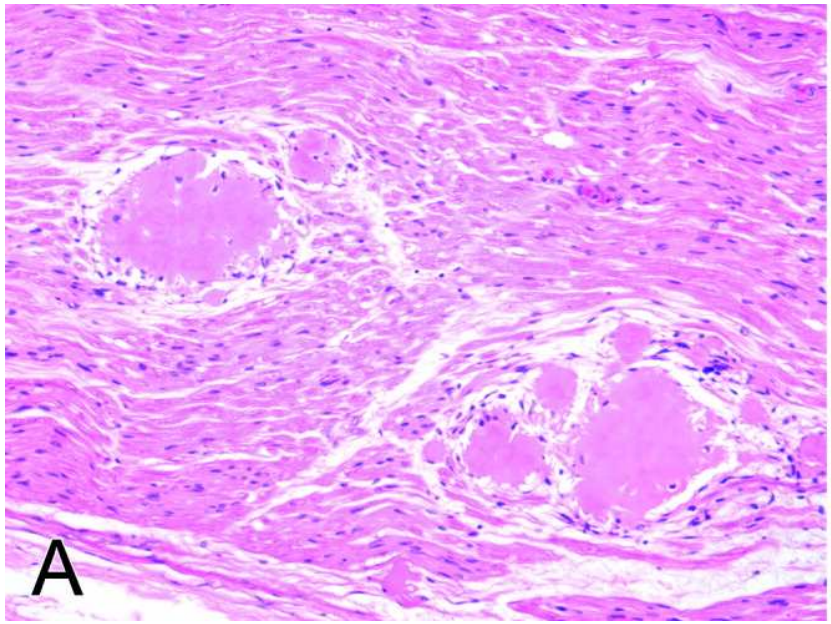
- Tissue biopsy to diagnose amyloid deposits
  - Fat aspirate
  - Involved organ
  - Gingival tissue or minor salivary gland
  - Sural nerve
- Amyloid Typing
  - AL
    - Bone marrow biopsy with immunohistochemistry for clonal plasma cells
    - Serum free light chain assay
    - Serum and urine immunofixation electropheresis
  - ATTR
    - DNA sequencing
  - AA
    - Immunohistochemistry
    - Identification of underlying infection, inflammatory disease

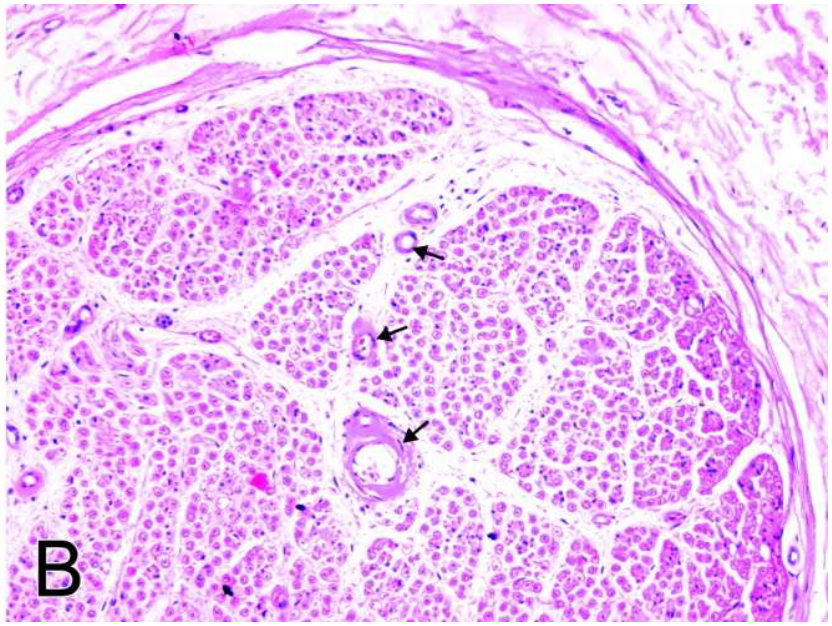
Tissue biopsy

- 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

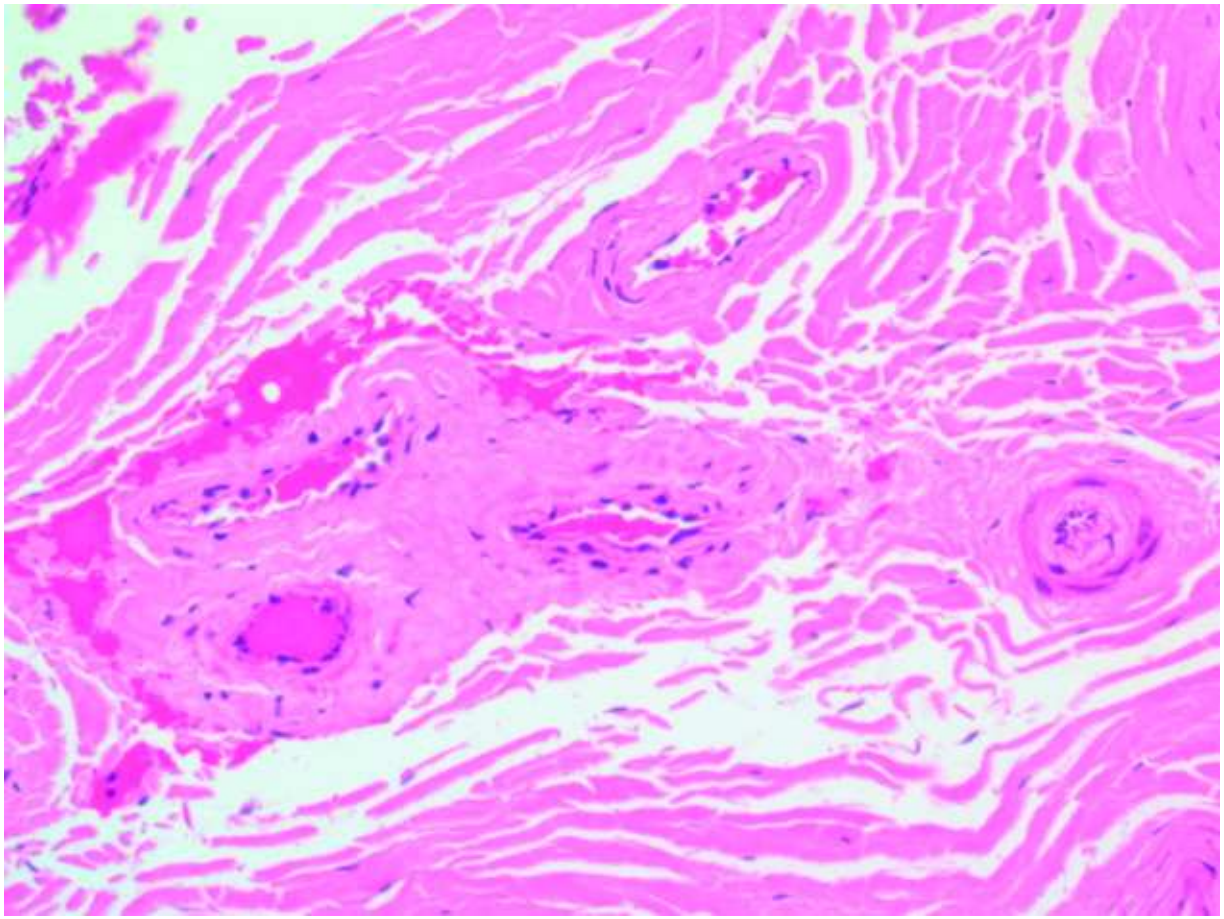
- Nerve involvement
- Intraneural amyloid
- AL amyloidosis cannot be differentiated from TTR amyloidosis on basis of biopsy
- Immunohistochemistry with specific Abs
  - Helpful for differentiation
  - Not completely reliable



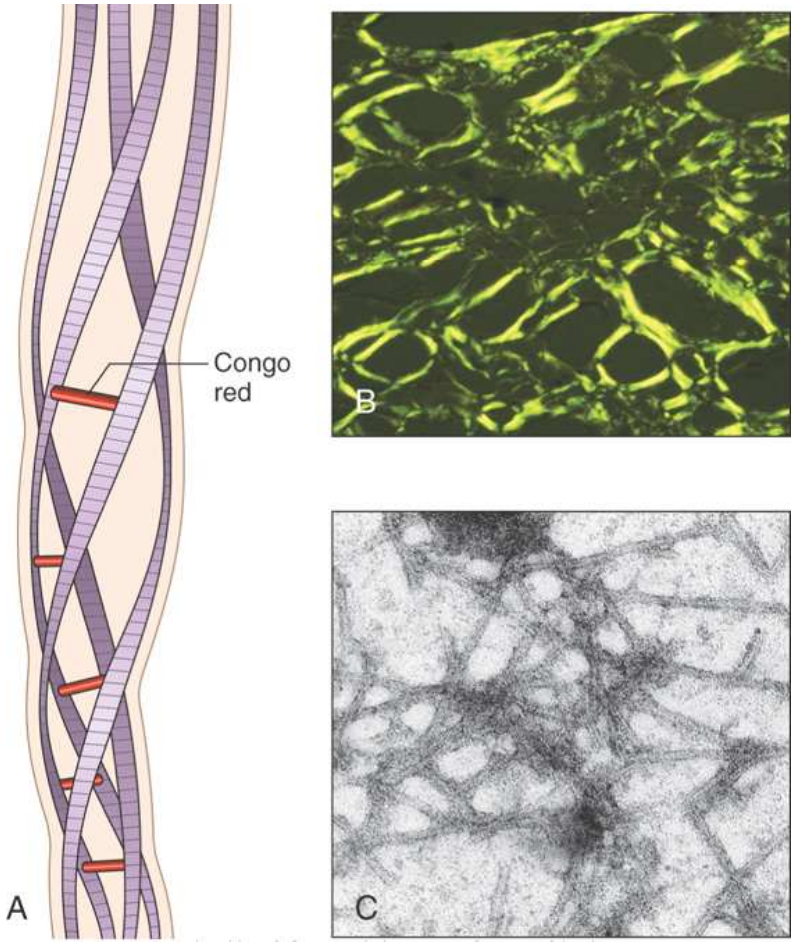


Sural Nerve Biopsy

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



Congo red staining



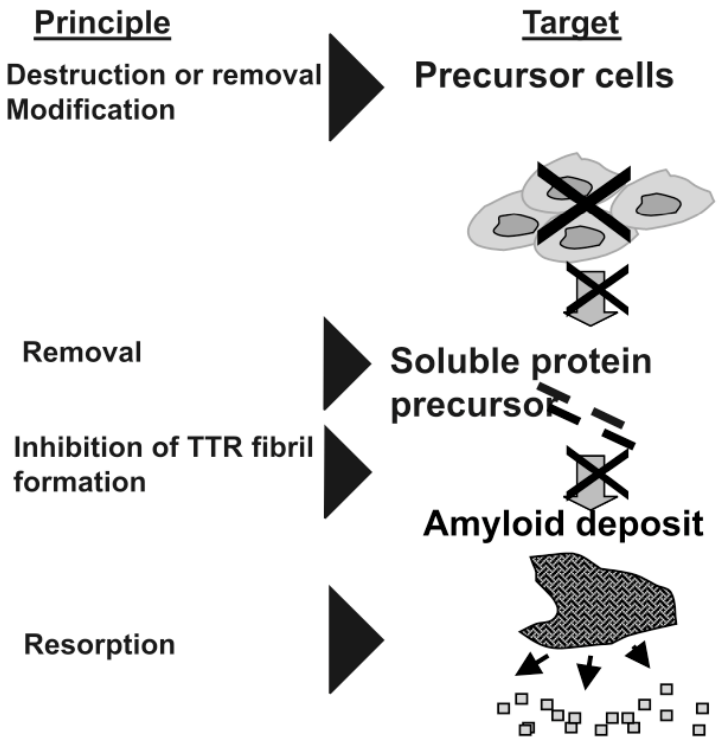
- Cross links within fibrils
- Polarized light
- Apple green birefringence

Commercial DNA Testing

- Available for TTR
  - Full TTR DNA testing if mutation unknown
  - Specific TTR sequence testing if mutation known
- Not available for:
  - ApoAI
  - Gelsolin

Treatment

Treatment Goals



Treatment

Liver transplantation (TTR-NAF) [1;27]
Chemotherapy (AL neuropathy) [15;45]
Ribozymes (TTR-FAP) [44]*

Plasma Exchanges

NSAI drugs (TTR-FAP) [30] *

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

	TTR-FAP	ApoA1	AL
Age at Onset	30s-70s	30s-40s	Usually older pts
Gender	M>F	M=F	M>F
Associated Systems	Sensorimotor Weight loss Heart failure Increased ICP Corneal Dystrophy	Sensorimotor Weight loss Renal Failure	Sensorimotor Weight loss Heart Failure Renal Failure
Family History	Yes	Yes	No
Cause of Death	Heart failure, wasting syndrome	Renal failure	Heart failure, arrhythmia, bleeding

Summary: Clinical Findings

Clinical manifestations

1. Progressive distal symmetrical sensory polyneuropathy
   Predominantly pain and thermal sensory loss (+++)
2. Progressive distal symmetrical sensorymotor polyneuropathy
3. Autonomic dysfunction
4. Other manifestations:
   Neuritis multiplex
   Carpal tunnel syndrome,
   Cranial neuropathy, ...

Context

A. Absence of diabetes
B. Positive family story of FAP
C. Monoclonal gammopathy (benign or malignant)

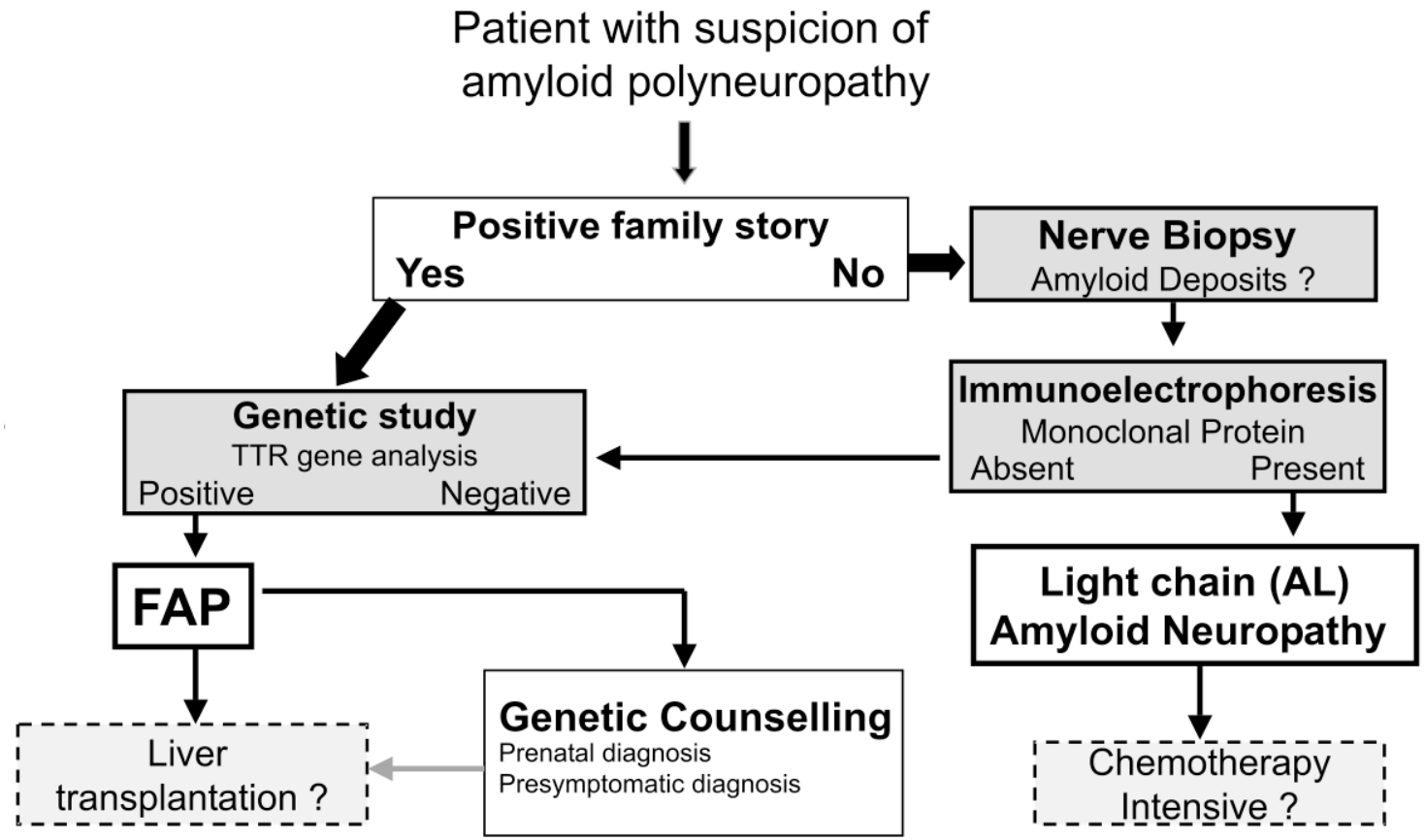
Electrophysiological study

D. Axonal pattern

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



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

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Thank you

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