Amyloidosis

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Amyloidosis

- Deposition of mis-folded proteins as insoluble fibrillary aggregates in extracelluar space in normal organs and tissues.
- Soluble in their normal folded configuration
- Pleated sheets in a zig-zag configuration
- Cross-β-pleated sheet of continuous non-branching fibrils oriented parallel to fibril axis comprise approximately 95% of the amyloid material.
- Serum amyloid P component and other glycoproteins bound, form 5% of amyloid material

Amyloidosis

- May be asymptomatic.
- Symptoms depend on magnitude and site of deposits.
- Pressure atrophy of adjacent cells results

Overview of systemic amyloidosis

Type of systemic amyloidosis	Amyloid protein	Underlying cause	Age of onset	Organs most commonly affected	Additional information
Light-chain amyloidosis	• Light chains of immunoglobulins → AL amyloid protein	• Plasma cell dyscrasias (e.g., multiple myeloma)	• > 40 years	• Heart • Kidney • Tongue • Autonomic nervous system • Gastrointestinal tract	• Most common form of amyloidosis in the western world • **Rapidly progressive clinical course**
Reactive amyloidosis	• Serum amyloid-associated protein (SAA) → AA amyloid protein	• Chronic inflammatory conditions (e.g., IBD, rheumatoid arthritis, SLE) • Chronic infectious diseases (e.g., tuberculosis, osteomyelitis) • Certain tumors (e.g., renal cell carcinoma, lymphomas)	• Any age	• Kidney • Adrenal glands • Liver and spleen • Gastrointestinal tract	• Most common form of amyloidosis in the developing world • The progression of the disease can be slowed by controlling the underlying condition.
Hemodialysis-associated amyloidosis	• β2-microglobulin → Aβ2M amyloid protein	• Long-term hemodialysis	• ~ 10 years after starting hemodialysis	• Joints and tendons	• Almost all individual on long-term hemodialysis will develop amyloidosis at some point

Localized amyloidosis

Affected organ	Amyloid protein	Associated condition
Senile cardiac amyloidosis	• Normal (wild-type) transthyretin (ATTR)	• Old age
Isolated atrial amyloidosis	• ANP → increased risk of atrial fibrillation	• Old age
Cerebral amyloidosis	• Aβ	• Alzheimer disease
	• APrP	• Prion diseases
Endocrine amyloidosis	• Islet amyloid polypeptide (IAPP) → amylin deposition in pancreatic islet	• Type 2 diabetes mellitus
	• Amyloid at insulin injection site (AIns)	• Subcutaneous insulin injection in diabetes mellitus
	• Procalcitonin (ACal)	• Medullary carcinoma of the thyroid

Hereditary amyloidosis

Condition	Amyloid protein	Pattern of inheritance	Age of onset	Affected sites	Additional information
Familial amyloid cardiomyopathy	• Mutated transthyretin (ATTR)	• Autosomal dominant disease (most common)	• > 20 years	• Ventricular endomyocardium → restrictive cardiomyopathy, arrhythmia	• Common in African Americans
Familial amyloid polyneuropathy (FAP)				• Peripheral and autonomic nerves	• Common in Portugal, Sweden, Japan, and among people of Irish descent

Familial Mediterranean fever (FMF)	• AA amyloid protein	• Autosomal recessive disease	• < 20 years	• Kidney
				• Liver and spleen
				• Adrenal glands
					• Common among individuals of Mediterranean descent (e.g., Sephardic Jews, Arabs, Turks)
					• Two types of FMF:
					  • Type 1 FMF
					  • Type 2 FMF

Systemic amyloidosis

- Usually involves:
- Kidney
- Proteinuria or nephrotic syndrome
- Heart
- Restrictive cardiomyopathy
- Dilated cardiomyopathy
- Orthostatic hypotension
- Conduction abnormalities
- Cardiac echocardiogram shows biventricular thickening with “granular sparkling” appearance
- Voltage diminished on EKG

Systemic amyloidosis

- Usually involves:
- GI tract
- Macroglossia
- Dysphonia
- Dysphagia
- Diarrhea
- Malabsorption

Systemic amyloidosis

- Neurologic system
- Peripheral neuropathy with painful paresthesias
- Autonomic dysfunction
- Impotence
- Skin
- Waxy, non-pruritic papules
- Periorbital ecchymoses
- “Pinch purpura” (skin bleeds with minimal trauma)

Systemic amyloidosis

- Lung
- Airway Obstruction
- Pleural effusion
- Liver
- Hepatomegaly without dysfunction
- Spleen
- Splenomegaly without leukopenia or anemia
- Factor X deficiency
- AL may bind Factor X

The most common types of amyloidosis and organ involvement					
Amyloid type	Heart	Kidneys	Liver/GI tract	PNS	ST
AL	++	++	+	+	+
ATTRm	++	–	–	++	–
ATTRwt	+++	–	–	–	Carpal tunnel
AFib	–	+++	–	–	–
AApoA1	+	++	++	+	–
ALys	–	+	++	–	–

Fig. 18.1

AApoA1, Apolipoprotein A1 amyloidosis; AFib, fibrinogen amyloidosis; AL, Light chain amyloidosis; ALys, lysozyme amyloidosis; ATTR, transthyretin amyloidosis; GI, gastrointestinal; m, mutant; PNS, peripheral nervous system; ST, soft tissue; wt, wild-type.

Localized amyloidosis

- Alzheimer's disease
- Dementia prominent
- Medullary carcinoma of the thyroid
- Type 2 diabetes mellitus
- Isolated atrial amyloidosis
- Hemodialysis related
- Carpal tunnel syndrome
- Joints

Localized amyloidosis

- Hereditary
- Neurologic system
- Heart
- Senile
- Heart
- Aorta
- GI tract

Primary amyloidosis

- Most common form
- 10-15% of all cases of amyloidosis
- AL type of amyloid
- Associated with:
- (1) Light chain disease (κ or λ)
- (2) Multiple myeloma (IgG)
- (3) Monoclonal gammopathy of unknown significance (GMUS)
- 2% of patients with these disorders will develop amyloidosis
- 50% will have cardiomyopathy

Primary amyloidosis

- (4) Waldenstrom's macroglobulinemia
- IgM overproduction (neoplastic B cells)
- Hyperviscosity syndrome
- Sensory neuropathy common (demyelination)
- Cardiac autonomic dysfunction in 36%
- Factor X deficiency (amyloid binding)

What is AL? Look for these symptoms

AL amyloidosis is caused by a bone marrow disorder. Amyloid proteins are produced by the plasma cells in the bone marrow. For AL amyloidosis, it is the "light chains" that become misfolded, and the abnormal, misfolded result is the forming of amyloid. These misfolded amyloid proteins are deposited in and around tissues, nerves and organs. As the amyloid builds up in an organ, nerve or tissue, it gradually causes damage and affects their function. Each amyloidosis patient has a different pattern of amyloid deposition in their body. It often affects more than one organ.

Nervous System

- Pain
- Numbness/Tingling
- Peripheral neuropathy
- Dizziness when standing
- Nausea/Diarrhea
- Erectile dysfunction
- Blood pressure/heart rate changes

Heart

- Stiff heart
- Thickened heart
- Shortness of breath
- Abnormal heartbeat
- Fatigue

Kidneys

- Chronic kidney disease
- Nephrotic syndrome
- Protein in the urine
- Edema
- Kidney failure

Digestive Tract

- Nausea
- Diarrhea
- Constipation
- Weight loss
- Loss of appetite
- Feeling of fullness

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Secondary amyloidosis

- Reactive
- AA type
- Cardiac involvement uncommon (5% of patients)
- Associated with:
- Inflammation
- Chronic infections
- Osteomyelitis
- Tuberculosis
- Rheumatoid arthritis (3% of patients)
- Inflammatory bowel disease
- Ankylosing spondylitis

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Common AA Amyloidosis Signs/Symptoms

- Swelling of ankles & legs
- Enlarged spleen, liver or thyroid
- Protein in the urine
- High cholesterol
- Renal failure
- Weight loss/Weakness
- Low blood pressure upon standing
- Diarrhea/Constipation

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Secondary amyloidosis

- Other malignancy
- Renal
- Hodgkin's disease
- Hereditary
- Familial Mediterranean fever
- Familial amyloid polyneuropathy

Hereditary amyloidosis

- Familial Mediterranean fever
- Recurrent fevers and serositis that resolves in 12-72 hours
- Presents in childhood or early teenage years
- Autosomal recessive
- Sephardic Jews, Armenians

Hereditary amyloidosis

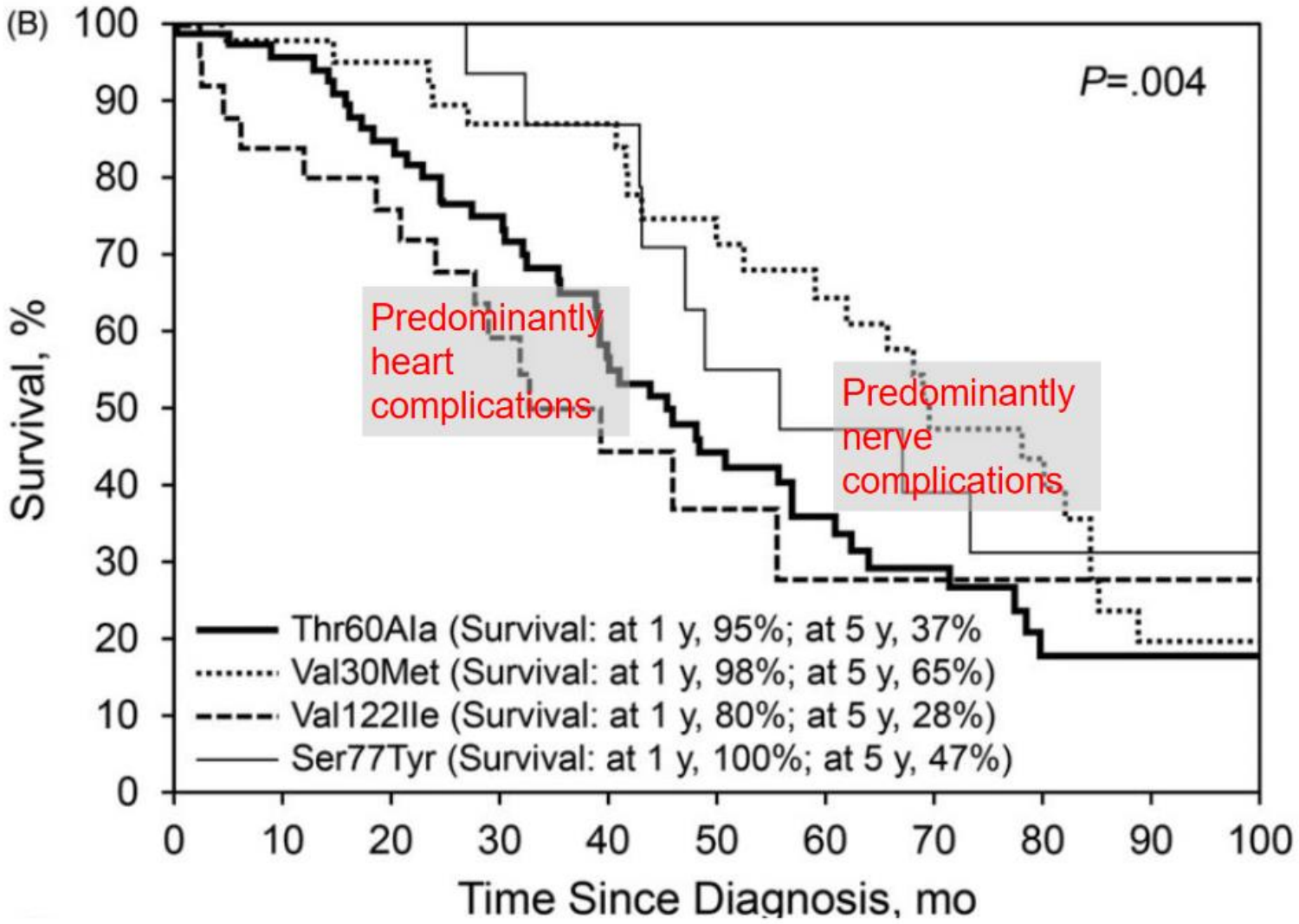
- MEFV gene at 16p13.3
- Met694Val mutation
- Reduces activity of pyrin protein, disrupting regulation of the inflammatory response (of neutrophils)
- Excess production IL-1
- AA type
- Colchicine therapy

Other genetic causes

- Apolipoprotein A-I (AApoAI)
- Apolipoprotein A-II (AApoAII)
- Gelsolin (Agel)
- Fibrinogen (Afib)
- Lysozyme (ALys)

Hereditary amyloidosis

- ATTR type
- Autosomal dominant (variable penetrance)
- Familial Amyloidic Polyneuropathy
- Deposition in axonal sensory autonomic and motor neuropathy
- $Val_{30}Met$ most common mutation
- Occurs before age 40 (endemic as in Portugal) or after 65 (sporadic)
- 50% develop cardiomyopathy
- Ocular involvement common (TTR produced in retina as well as liver)
- Renal disease rare



https://www.alnylam.com/web/assets/03-hATTR_Patisiran_RDDay-2016.pdf
Accessed 01/20/2020

Hereditary amyloidosis

- Familial Amyloidic Cardiomyopathy
- Abnormalities in long-axis function of both ventricles precede the impairment of circumferential ventricular function
- Restrictive disease in late stages
- May involve valves
- Arrhythmias common
- $Leu_{111}Met$ mutation common in Danes (not in Swedes)
- $Val_{122}Ile$ mutations in 4% of sub-Saharan Africans
- Appalachian amyloid of $Thr_{60}Ala$ mutation

Hereditary amyloidosis

- Leptomeningeal form
- ATTR gene mutation at 18q12.1
- Amyloid origin is from choroid plexus, not liver
- Cerebral amyloid angiopathy

- All hereditary forms have 10-20 year life spans following presentation

Hemodialysis associated amyloidosis

- $A\beta_{2m}$ type.
- β_2-microglobulin is a component of MHC I molecules and is present on the surface of nucleated cells
- Normal serum component as well
- β_2-microglobulin is normally filtered through the glomerulus and catabolized in proximal tubules

Hemodialysis associated amyloidosis

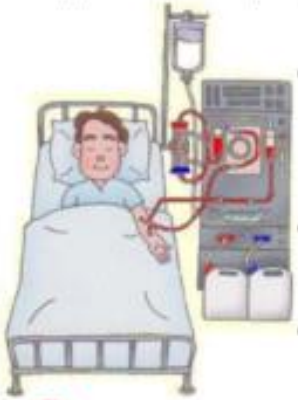
- As hemodialysis is equivalent to a GFR of 10ml/min, β_2-microglobulin accumulates
- Not filtered by the dialysis membrane
- Usually presents as carpal tunnel syndrome

Aβ2M Amyloidosis

βeta-2 Microglobulin is a protein that can build up in the blood as a result of kidney failure. βeta-2 Microglobulin Amyloidosis (Aβ2M) has emerged as a major complication and a disabling condition of long-term hemodialysis (HD).

Studies show that Aβ2M affects 95% of patients that have been treated with hemodialysis for more than 15 years, but it can also occur in patients who use continuous ambulatory peritoneal dialysis (CAPD).
Symptoms include:

- Carpal Tunnel
- Joint Pain/Stiffness
- Soft Tissue Masses
- Bone Cysts/ Fractures
- Irregular Heartbeat (arrhythmia)



- Paraplegia if on dialysis 20-30 years
- Congestive Heart Failure (rare)
- Gastrointestinal Bleeding (rare)

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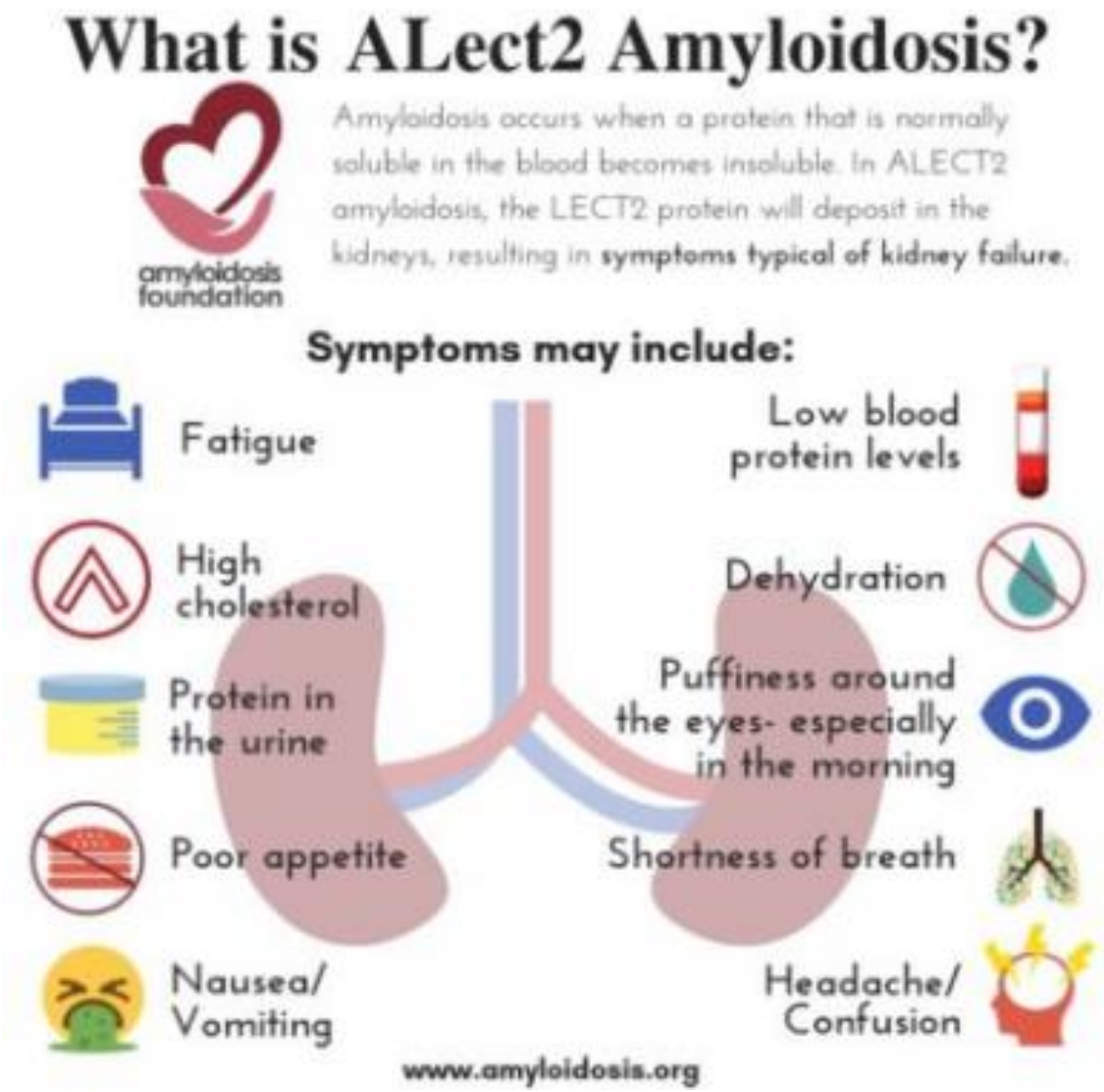
Senile amyloidosis

- Wild type ATTR
- Normal non-mutated transthyretin deposited
- >75 years old
- Cardiomyopathy major presentation (infiltrative)
- However, rupture of the biceps tendon or lumbar spine involvement may precede cardiac presentation by years



Recently described in elderly Mexicans. Presents with renal problems but with benign sediment.

Also affects liver.

Localized amylodosis

- Localized amyloid deposits in the airway (trachea or bronchus), eye, or urinary bladder are often caused by local production of immunoglobulin light chains, not originating in the bone marrow.
- Localized AL can be treated with radiation therapy

TYPE	PROTEIN	DERIVED FROM
Primary	AL	Immunoglobulin
Secondary	AA	Serum amyloid associated protein (synthesized in liver); acute phase reactant
Familial: Polyneuropathy Cardiomyopathy Leptomeningeal	ATTR	Liver Liver Choroid plexus
Senile cardiac	ATTR Wild type AANP	Transthyretin Atrial natriuretic peptide
Diabetes Mellitus type 2	Amylin (calcitonin family)	Islet amyloid peptide co-secreted with insulin
Medullary Carcinoma of the Thyroid (Sporadic or MEN)	Calcitonin	Calcitonin
Alzheimer's Disease	Aβ	Amyloid precursor protein
Dialysis associated	β_2-microglobulin	MHC I molecule

Major forms of amyloid

- AL
- N- terminal fragments of light chains, principally λ, or intact light chains, or both
- Secreted by monoclonal population of plasma cells
- AA
- Proteolyzed form of liver produced serum amyloid associated (SAA) protein in response to inflammation
- Not an immunoglobulin homologue
- Bound to HDL (high density lipoprotein)
- IL-1, IL-6 stimulate

Major forms of amyloid

- Aβ
- Proteolyzed amyloid precursor protein
- Characteristic of Alzheimer's disease and cerebral amyloid angiopathy
- Transthyretin
- Transport thyroxin and retinol
- Mutants in familial amyloidosis
- Wild type in senile amyloidosis
- β_2-macroglobulin
- Normal serum protein also a component of MHC I molecules
- Not well filtered by hemodialysis membranes

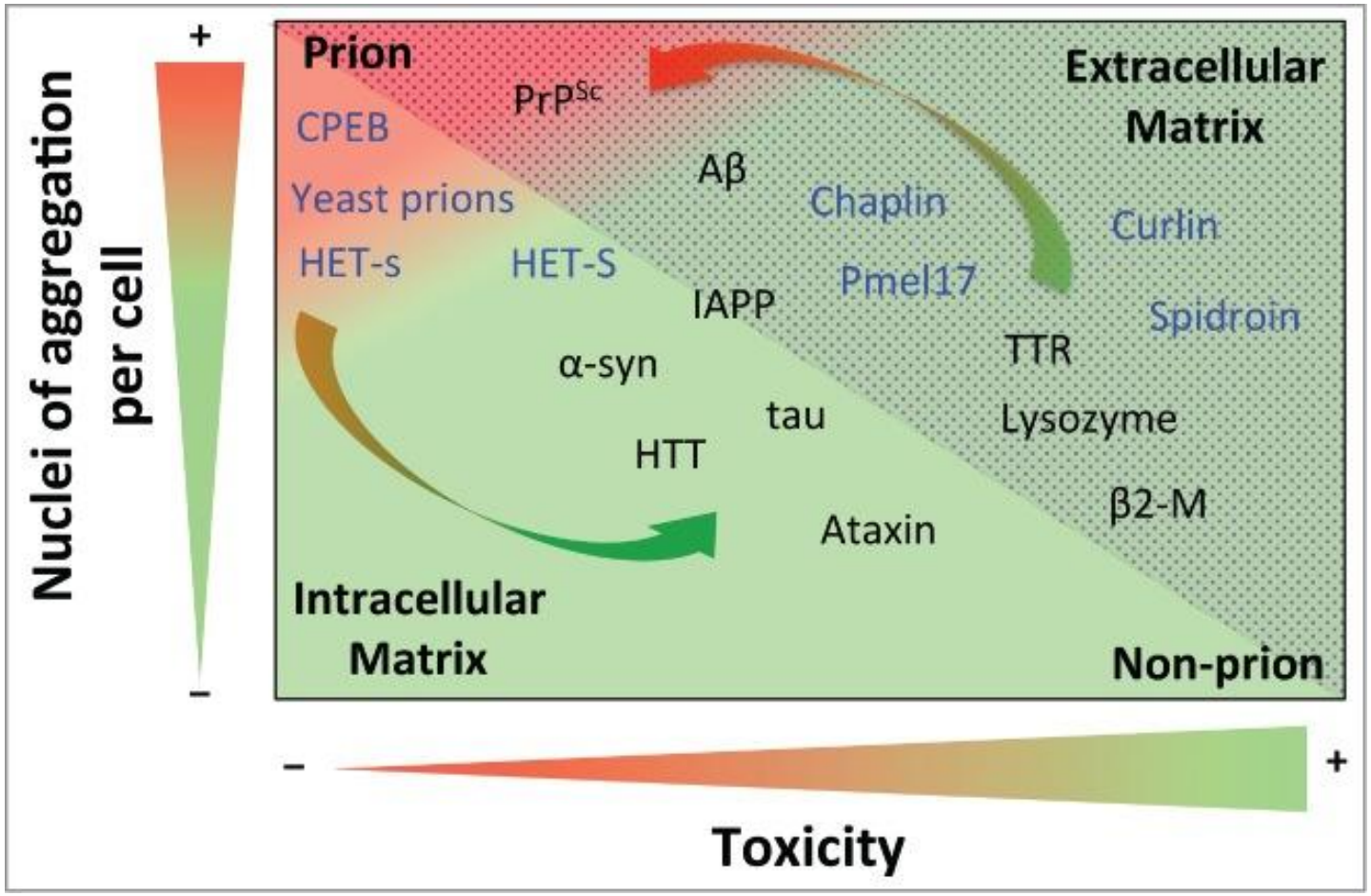
Major forms of amyloid

- Calcitonin
- Medullary carcinoma of thyroid
- Amylin (Islet Associated Protein)
- Type II diabetes mellitus

Major forms of amyloid

- Prion proteins
- Amyloids in which the aggregating process has become self-perpetuating and infectious
- High numbers of aggregating nuclei associated with infectivity
- Classic prions (associated with transmissible spongioform encephalopathies) colonize lymphoreticular organs followed by release of cell-free oligomeric or protofibril molecules whose predilection is peripheral nerves and the CNS
- PrP oligomers are the most cytotoxic PrP species.
- PRNP gene at 20p13 (Copper transport)

Prion proteins and infectivity



Sabate, R, "When amyloids become prions," Prion (2014) 8:233-239
doi: 10.4161/19336896.2014.968464 Accessed 12/10/2019

Alzheimer's disease

- Alzheimer Disease is the cause of approximately 50% of the clinical dementias in the elderly.
- 1% prevalence 60-65 years of age.
- Doubles yearly.
- 5-10% familial.
- Autosomal dominant
- Mutations in the APP gene are the most common cause of Alzheimer's disease as well as cerebral amyloid angiopathy.
- Aβ protein is result of APP mutation at 21q21.3

Alzheimer's disease

- The Aβ portion of the transmembrane APP extends from the extracellular region into the transmembrane domain.
- If cleaved at the cell surface by α-secretase, and then cleaved within the membrane by γ-secretase, a soluble fragment is created (soluble β-amyloid)
- If cleaved at the cell surface by β-secretase, and then cleaved within the membrane by γ-secretase, the portion may be paired with one cleaved by α-secretase and form the Aβ-peptide.

Alzheimer's disease

- $A\beta_{40}$ and $A\beta_{42}$ are abnormal monomers that result
- This form is highly prone to aggregation.
- The peptide is directly neurotoxic (β-amyloid).
- Initially phagocytized;
- However, microglia are chronically activated and secrete IL-1, IL-6, and TNF
- Microglial receptors for advanced glycation end products also bind Aβ peptide, further amplifying cytokine production

Aβ

- Vascular dysfunction caused by cerebral amyloid angiopathy reduces perivascular Aβ clearance
- Aβ accumulates
- Factors that favor vascular Aβ deposition over parenchymal deposition include:
- $Aβ_{40}$ (termination of Aβ at or before position 41)
- Missense mutations within the Aβ coding region
- Co-deposited proteins, such as fibrinogen.

Alzheimer's disease

- Soluble β-amyloid binds to the receptor found on both immune cells and neurons (LilrB) .
- The bound complex activates cofilin which begins to degrade actin and leads to synapse disassembly.
- LilrB is a means to check synapse strengthening
- Insoluble β-amyloid protein accumulates in neurons, glial cells, and vessel walls.
- BUT, 30% of patients do not have amyloid.
- AND many "normals" who have amyloid do not have dementia.

APP gene

- Amyloid-β (Aβ) in the brain interstitial fluid can be cleared via perivascular drainage pathways or deposited as neuritic plaques in the brain parenchyma or as cerebral amyloid angiopathy along vessel walls.
- A picture of progressive dementia is also seen in Down's syndrome.
- APP gene

Histopathology

- There is no consistent or distinctive pattern of distribution of amyloid in organs.
- Deposits show apple-green birefringence on Congo-red stain.

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Organ histopathology

- Kidney
- Most common and most serious form of involvement
- Mesangium
- Peritubular interstitium
- Arteriolar walls
- Spleen
- Two distinct patterns
- Splenic follicles
- Granular appearance (sago spleen)
- Sinuses and connective tissue
- Fuse into map like areas (lardaceous spleen)

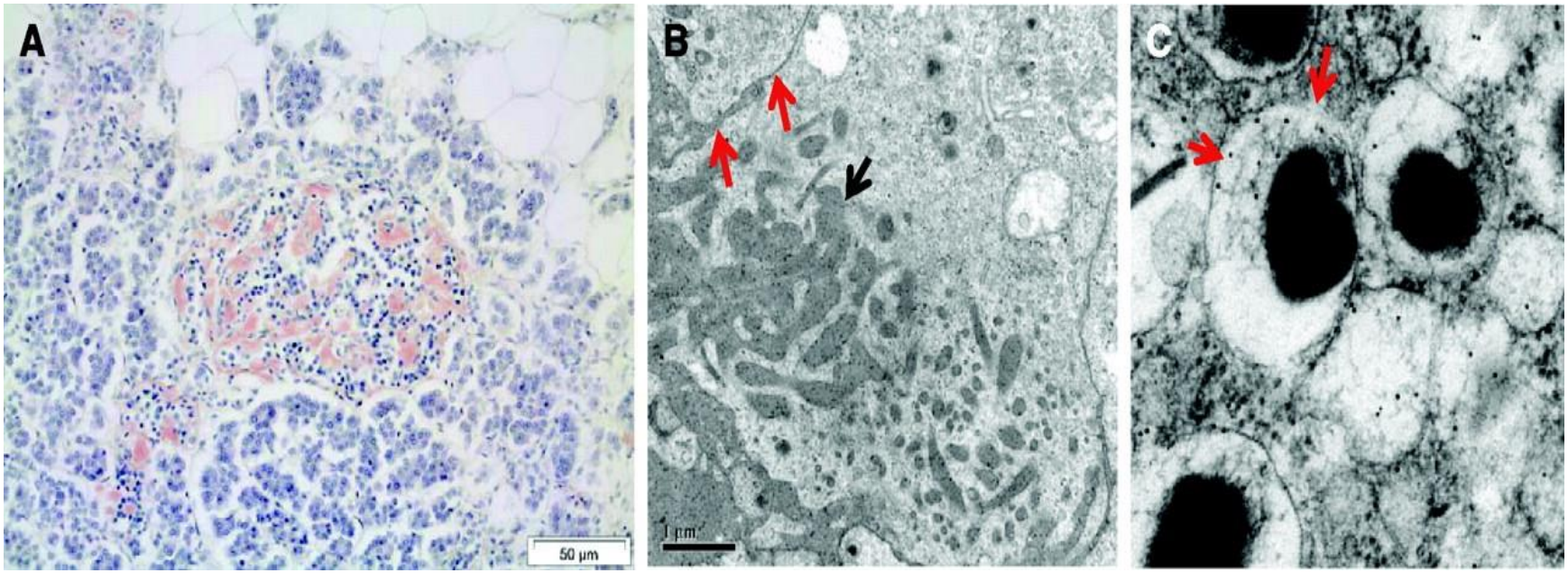
Organ histopathology

- Liver
- Space of Disse
- Pressure atrophy leads to parenchymal replacement
- Vascular involvement
- Deposition in Kuppfer cells
- Heart
- Subendocardium
- Myocardium
- Vessels

Organ histopathology

- Brain
- Senile dementia
- β-amyloid in arteriolar walls
- Alzheimer's
- Neuritic plaques
- Dystrophic neurites around Aβ amyloid core
- Diffuse plaques
- Aβ amyloid deposition without neurites
- β-amyloid in arteriolar walls

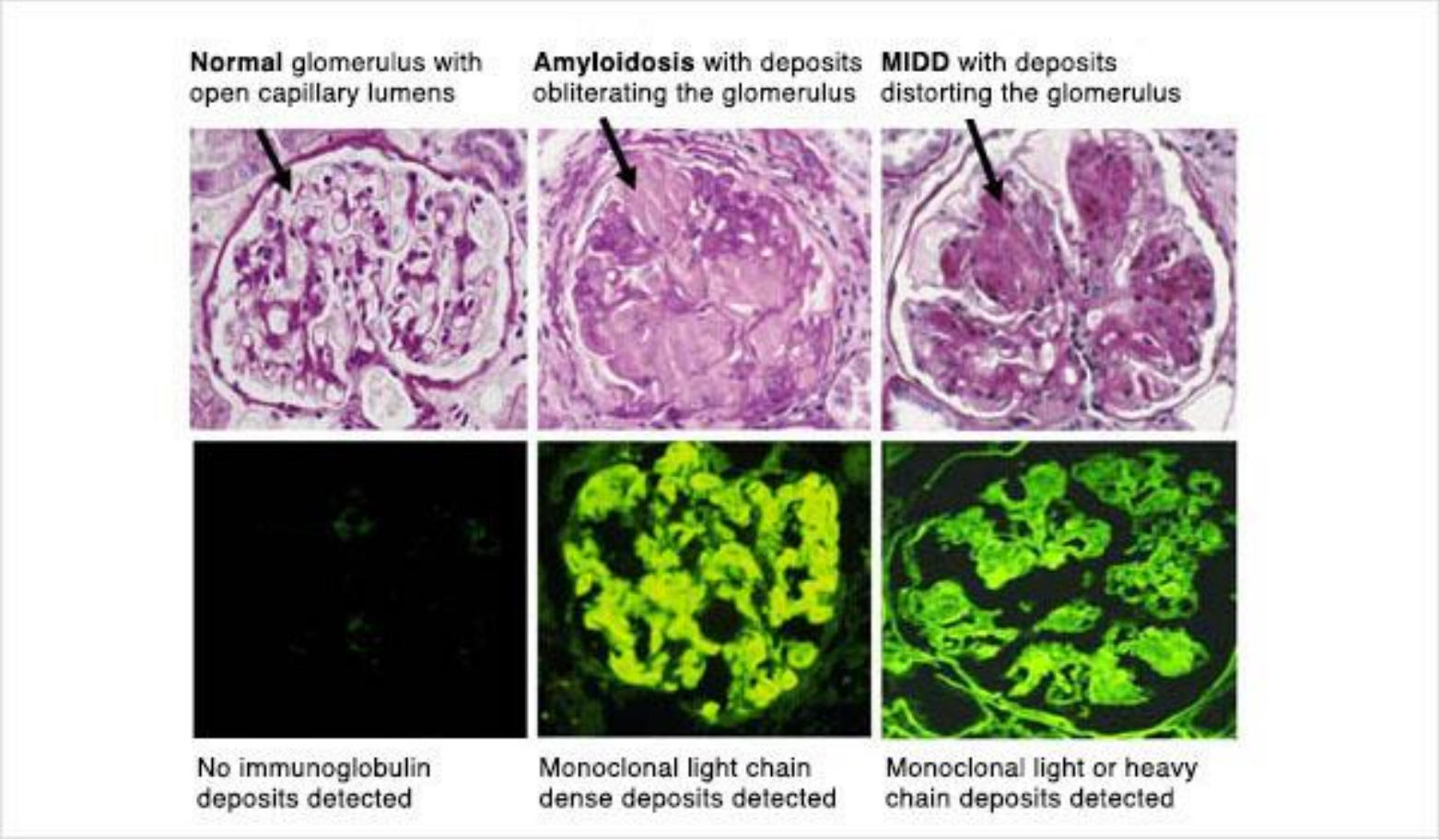
Type 2 diabetes mellitus



Amylin is co-produced with β-cells. Degraded by neprilysin. Lesion is not present in type 1 diabetes mellitus. Calcitonin family. There is an IAPPS20G mutation in Asians.

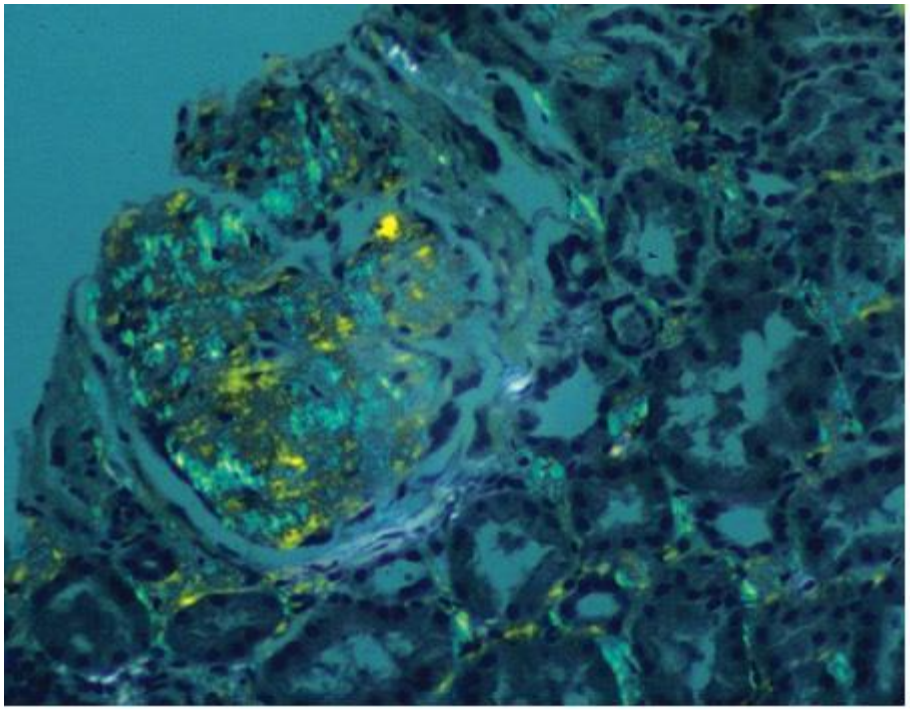
Westmark, P, Andersen, A, Westermark, GT, “Islet amyloid polypeptide, islet amyloid, and diabetes mellitus,” Physiological Reviews (2011) 91:795-826
doi.org/10.1152/physrev.00042.2009
Accessed 12/10/2019

Amyloid in kidney



https://unckidneycenter.org/files/2017/10/amyloidosis-lm-and-im.jpeg
Accessed 12/06/2019

Amyloid in kidney



Amorphous, acellular expansion of the mesangium, with material often also infiltrating glomerular basement membranes, vessels, and in the interstitium.

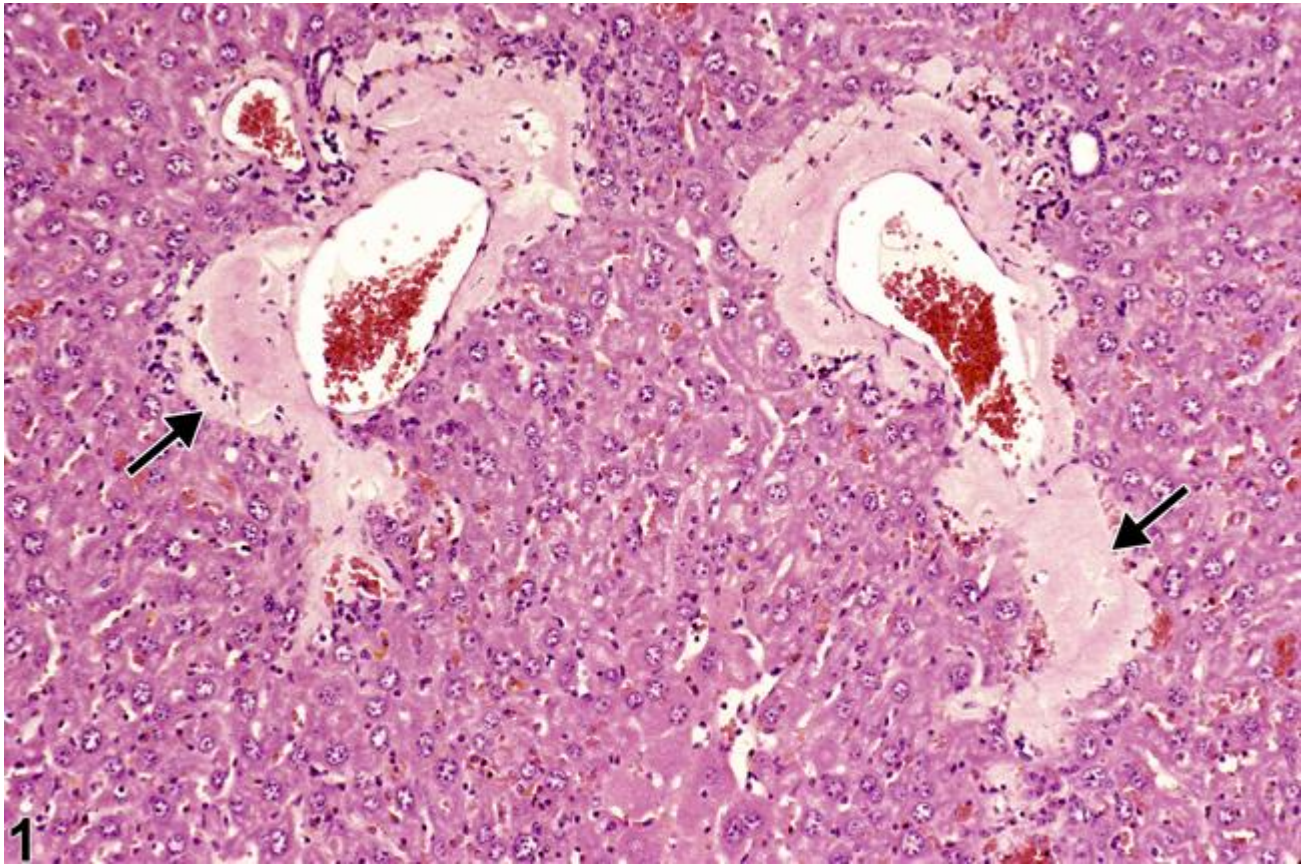
Apple-green birefringence by polarized Congo red stain.

The deposits are composed of randomly organized 9- to 11-nm fibrils by electron microscopy.

(ABF/Vanderbilt Collection.)

Fig. e9-13 Accessed 03/17/2010

Amyloid in liver



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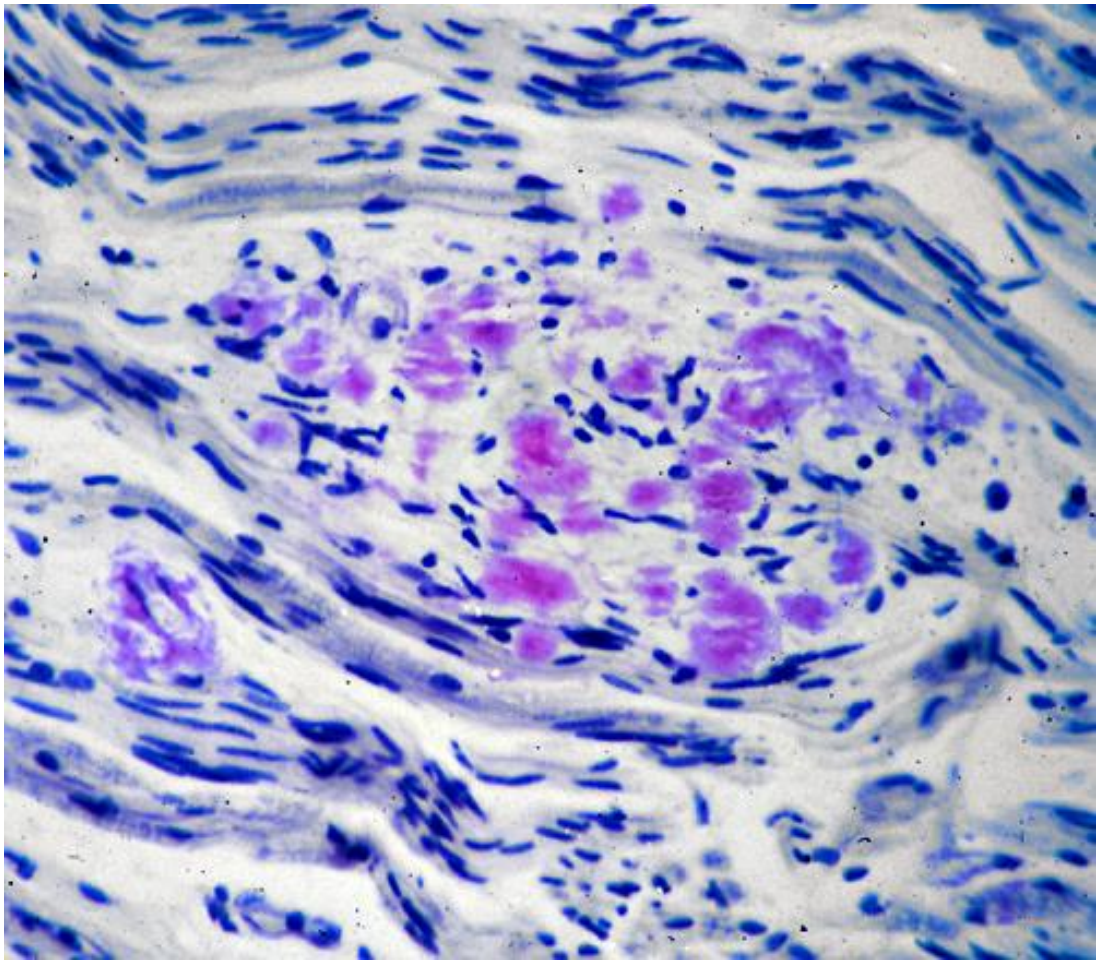
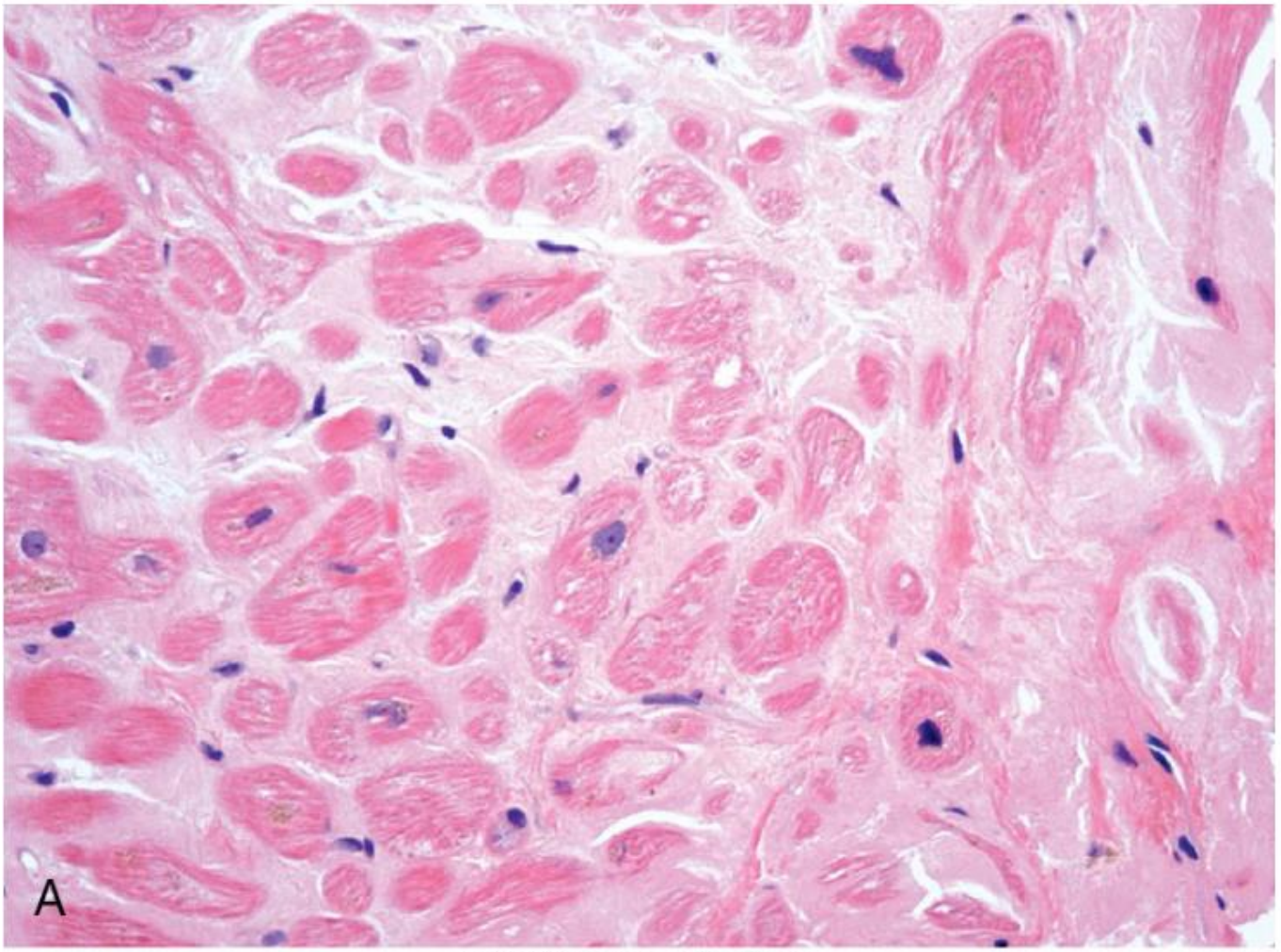
Amyloid in peripheral nerve



http://neuropathology-web.org/chapter12/images12/12-amyloid.jpg
Accessed 12/06/2019

Amyloid deposition in heart



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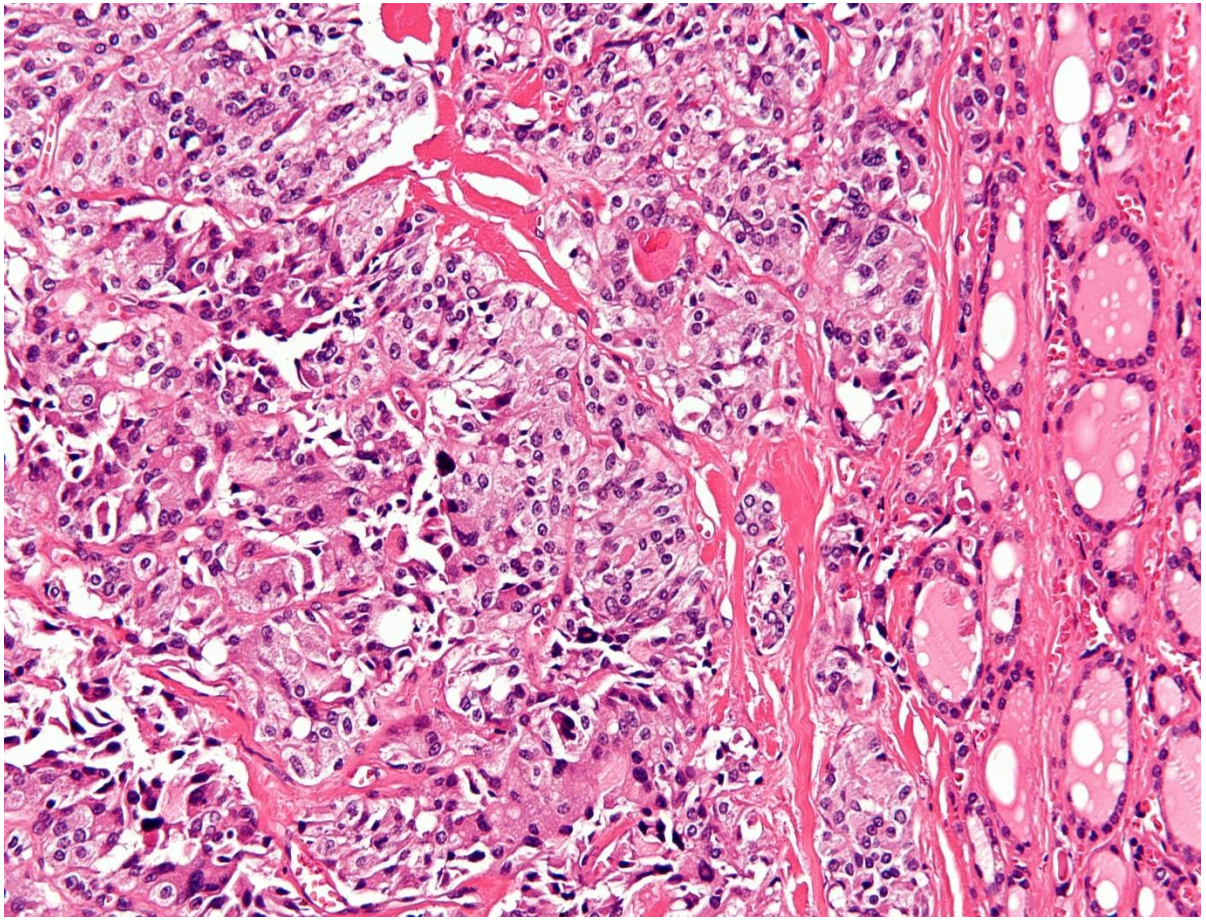
Accessed 12/06/2019

Medullary carcinoma of thyroid

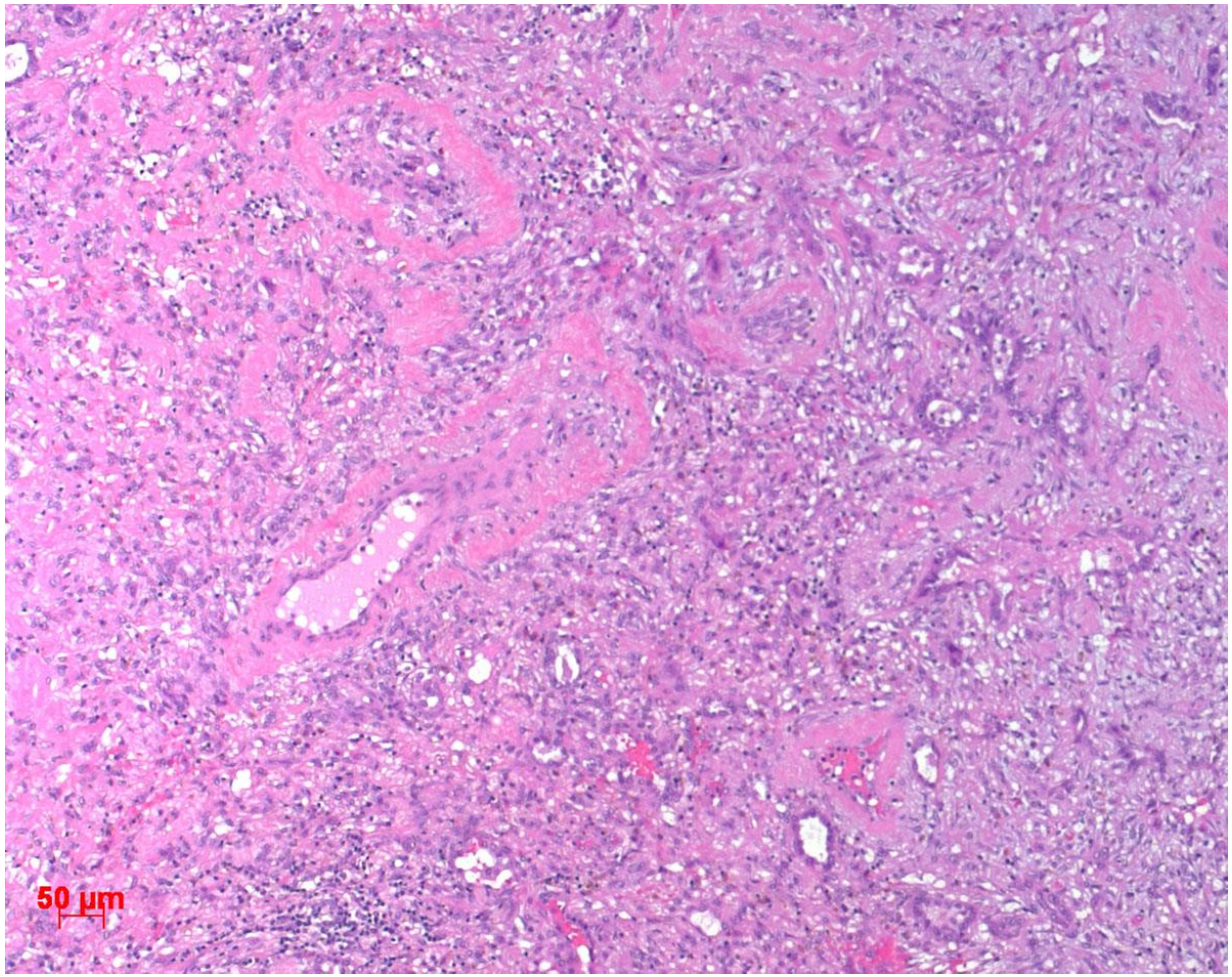


Amyloid deposition in medullary carcinoma (left) with compressed thyroid tissue on right

https://upload.wikimedia.org/wikipedia/commons/0/0b/Medullary_thyroid_carcinoma_-_high_mag.jpg

Accessed 12/10/2019

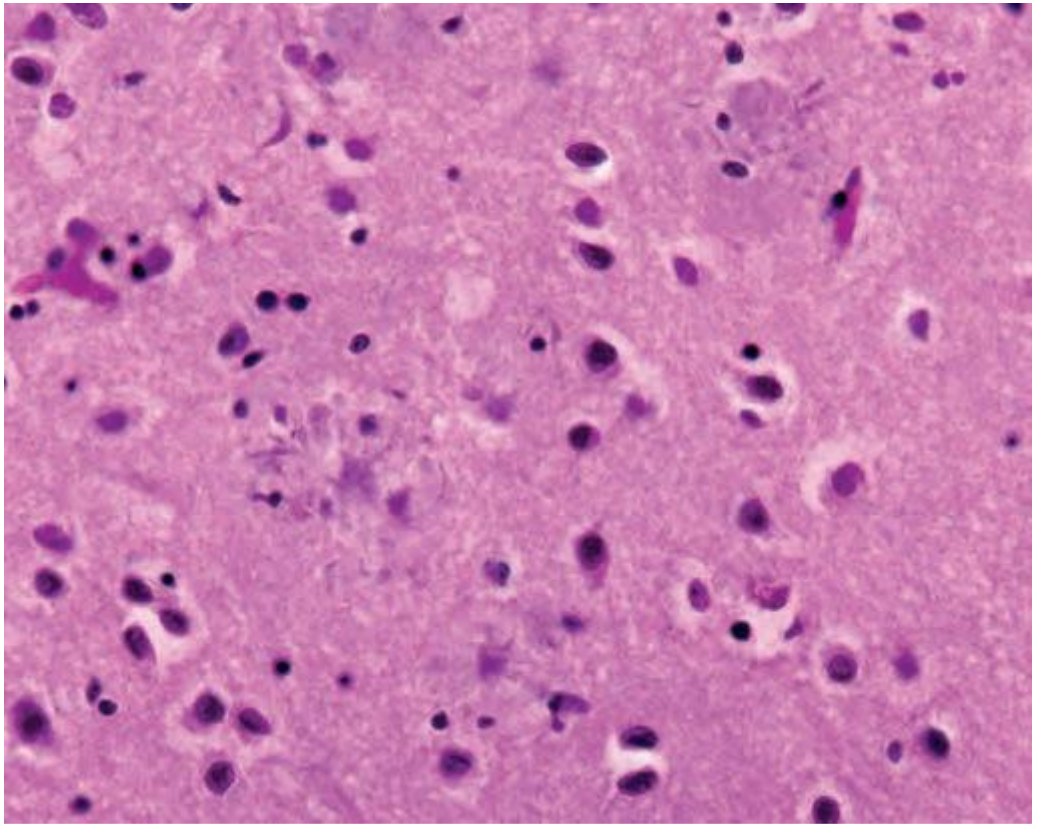
Amyloid deposition in lung



https://www.pathologyportal.org/105th/images/pulm0304.jpg
Accessed 12/06/2019

Amyloid deposition in brain

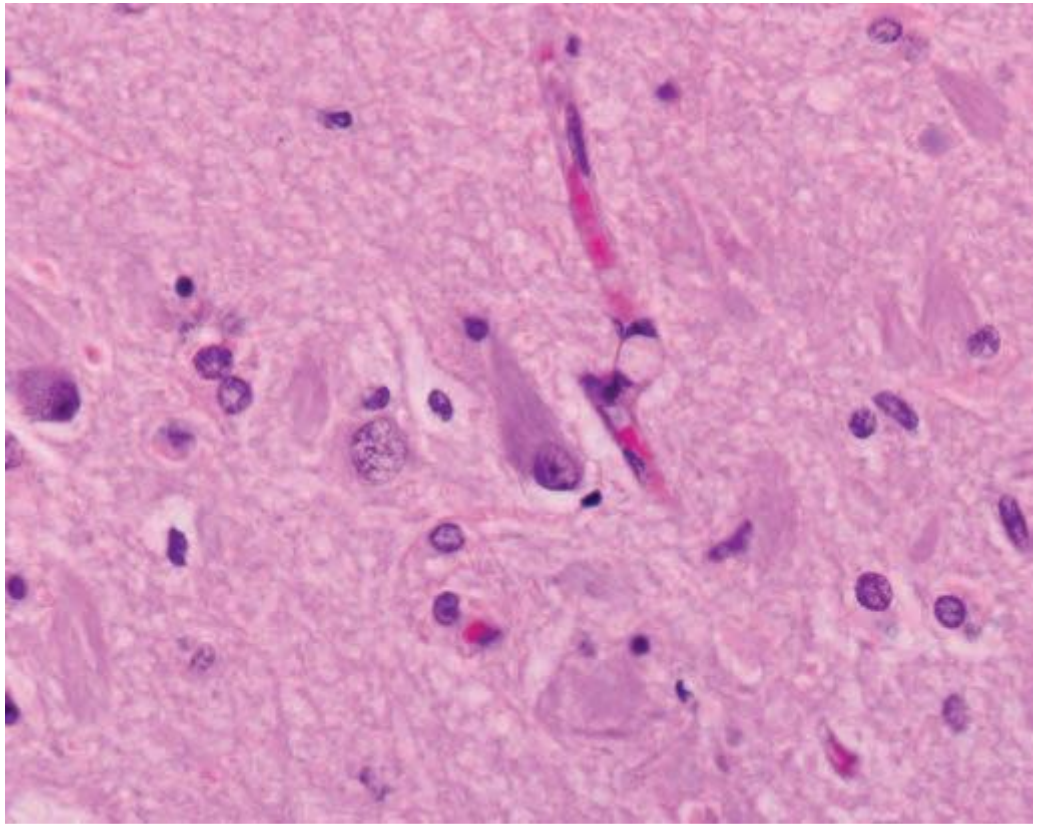
Plaques with dystrophic neurites surrounding amyloid cores are visible



Frosch, MP, Anthony, DC, De Girolami, U, “The Central Nervous System,” in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 28-13A Accessed 10/25/2019

Amyloid deposition in brain

Neurofibrillary tangle is present within one neuron, and several extracellular tangles are also present



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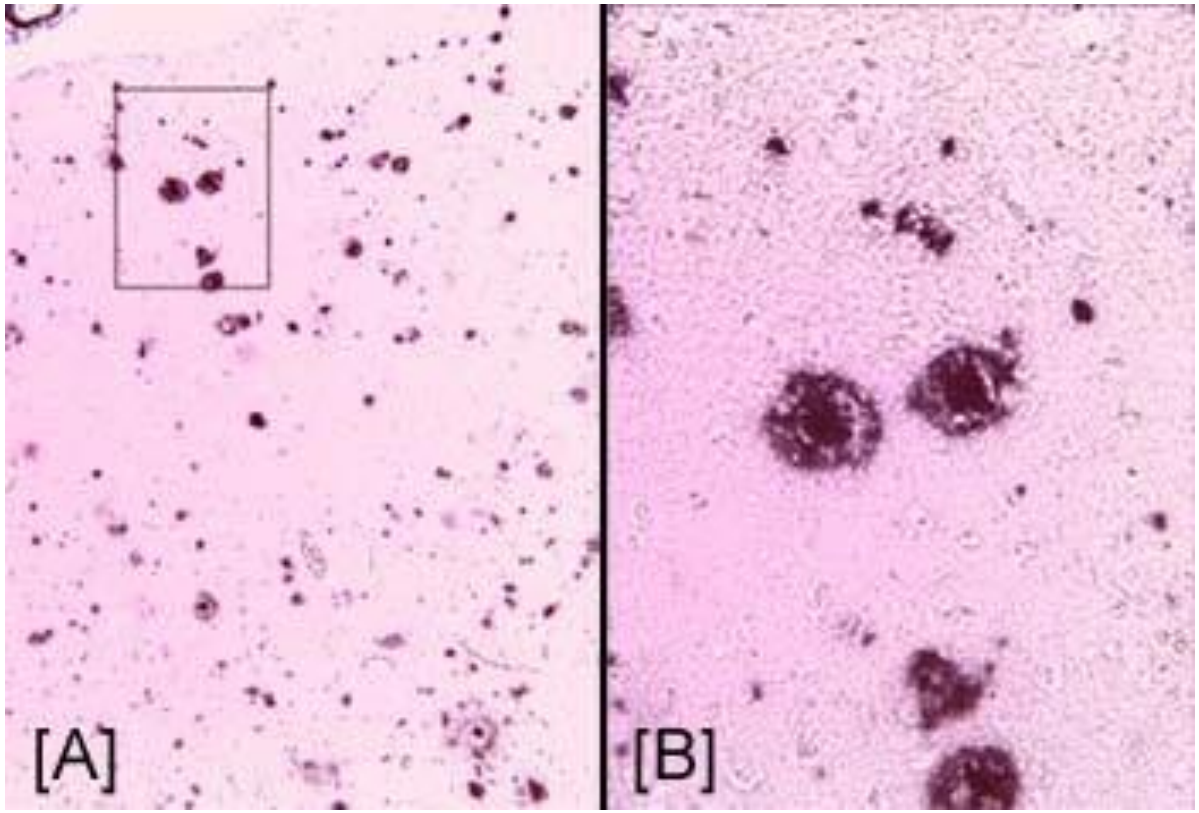
Amyloid deposition in brain

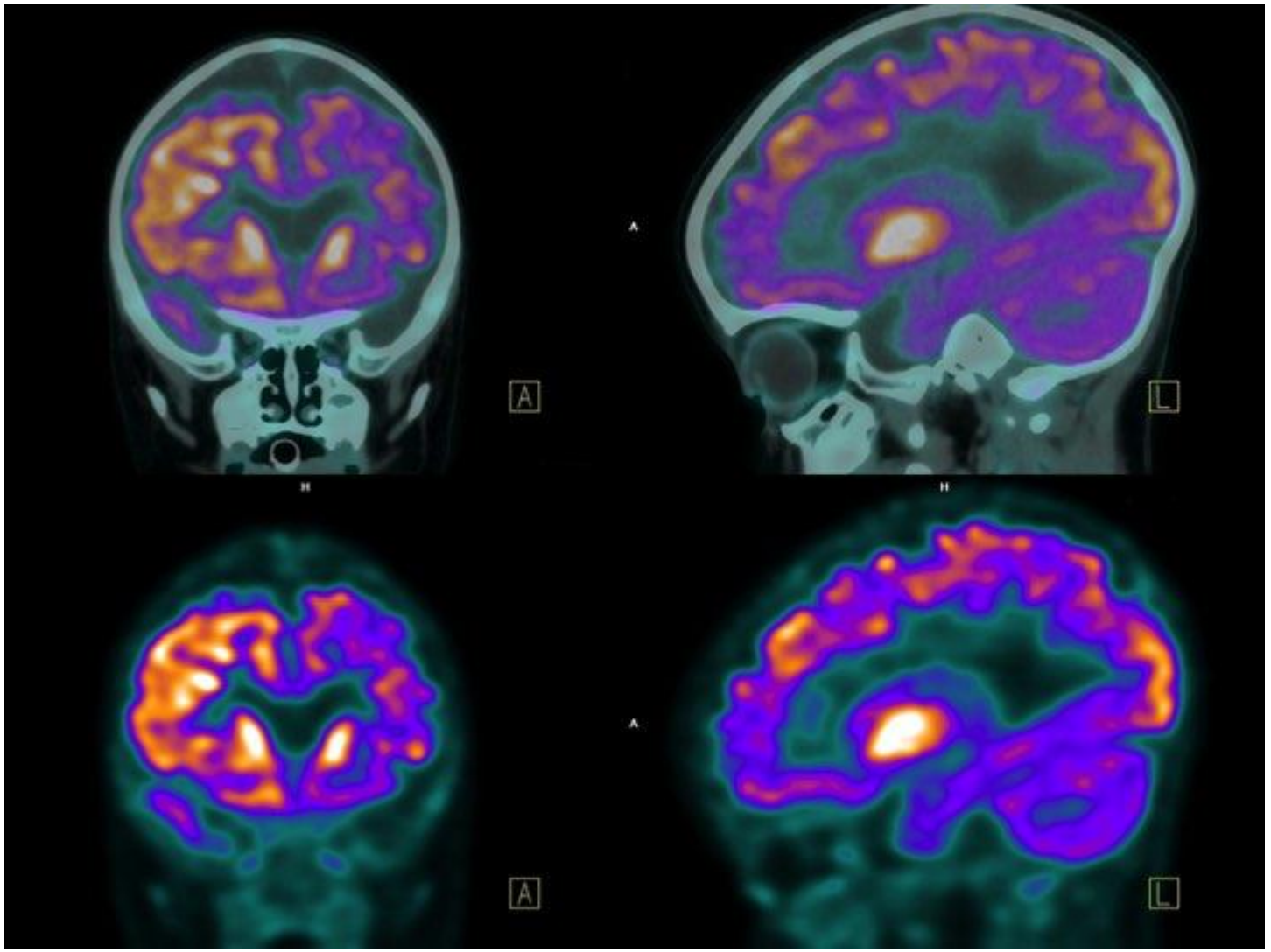


https://www.abcam.com/ps/products/12/ab12267/Images/ab12267-19802-anti-beta-amyloid-1-42-antibody-immunohistochemistry.jpg
Accessed 12/06/2019

Diagnostic studies

- First exclude primary amyloidosis (myeloma)
- Serum and urine immunoelectrophoresis
- Neither serum or urine electrophoresis or screen for free light chains in urine (Bence-Jones proteins) as sensitive or specific
- If immunoelectrophoresis positive, bone marrow biopsy
- Scintigraphy with radiolabeled SAP
- Also provides information as to extent of disease
- Biopsy of abdominal subcutaneous fat pad or of rectum or of gingiva in secondary amyloidosis
- Genetic testing for hereditary forms

Amyloid scan



https://clf1.medpagetoday.com/media/images/61xxx/61254.jpg Accessed 20/06/2019

Treatment and outcomes

- Systemic amyloidosis
- Bortezomib with cyclophosphamide and dexamethasone followed by tandem stem cell transplant if limited organ dysfunction
- If there is cardiac disease, treat with diuretics.
- If appropriate, implantable device
- Avoid digoxin
- calcium channel blockers
- vasodilators
- Median survival in primary amyloidosis is 12-18 months post diagnosis
- if cardiac involvement, 6 months

Treatment and outcomes

- Secondary amyloidosis
- Treat underlying disease
- Colchicine for Familial Mediterranean Fever to prevent progression of renal disease
- Median survival for secondary amyloidosis is 11 years post diagnosis
- Hereditary amyloidosis
- Liver transplant if site of precursor protein production is in liver to prevent further deposition
- Median survival is 10-20 years post diagnosis