Amyloidosis

Whiteboard Tutorial

Tute Map Checklist –

By the end of this tutorial you should know:

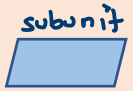
What is amyloid?
Local v Systemic
Systemic Amyloidosis Types

For each type of amyloid know:
Precursor protein
Major organs involved
Major organ manifestations
Basic Diagnostic Approach

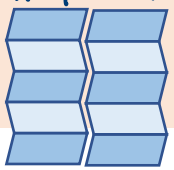
1. Clinical Suspicion
2. Find Amyloid
3. Find Precursor Protein
4. Treatment

Systemic Amyloidosis

1. What is Amyloid?



misfold



How do you know it's amyloid?

- congo red +
- applegreen birefringence.

If all amyloid looks the same on biopsy…

How do you clarify the precursor?

- GOLD STANDARD mass spectrometry proteomics.
- staining for precursor

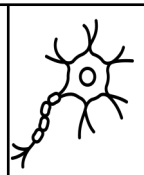
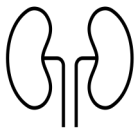
Which type of cardiac amyloid can be diagnosed using a bone scan?

- ATTR.

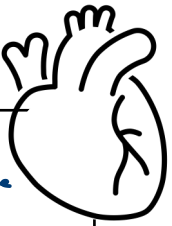
No biopsy needed!

Cardiac Biopsy
= tricky cases

Common Organs Affected

Precursor (Blood)	Amyloid (tissue)				Other
light chains κ/λ	AL	✓	✓	✓	
transthyretin	ATTR.	* ✓	* ✓	✗	carpal tunnel. Bilateral.
serum amyloid A	AA.	✗	✗	rare ✓	+ GI 30%
(Dialysis) β2 microglobulin	Aβ2M.	✗	✗	✗	 MSK

cardiac MRI
- ?amyloid – yes / no
- Late gadolinium enhancement diffuse / global.



- ⇒ HFpEF
- ⇒ AF / arrhythmia
- ⇒ conduction abnormalities

ECHO
- LV mass ↑
- Diastolic Dysf.
- ↓ global longitudinal strain with apical sparing ← ?amyloid.

BNP / Troponins
⇒ severity / prognostic.

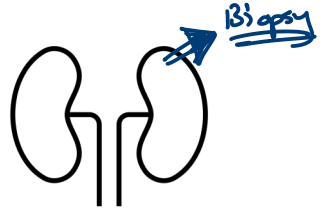
Ulnar N.

Sural nerve

Autonomic dysfunction

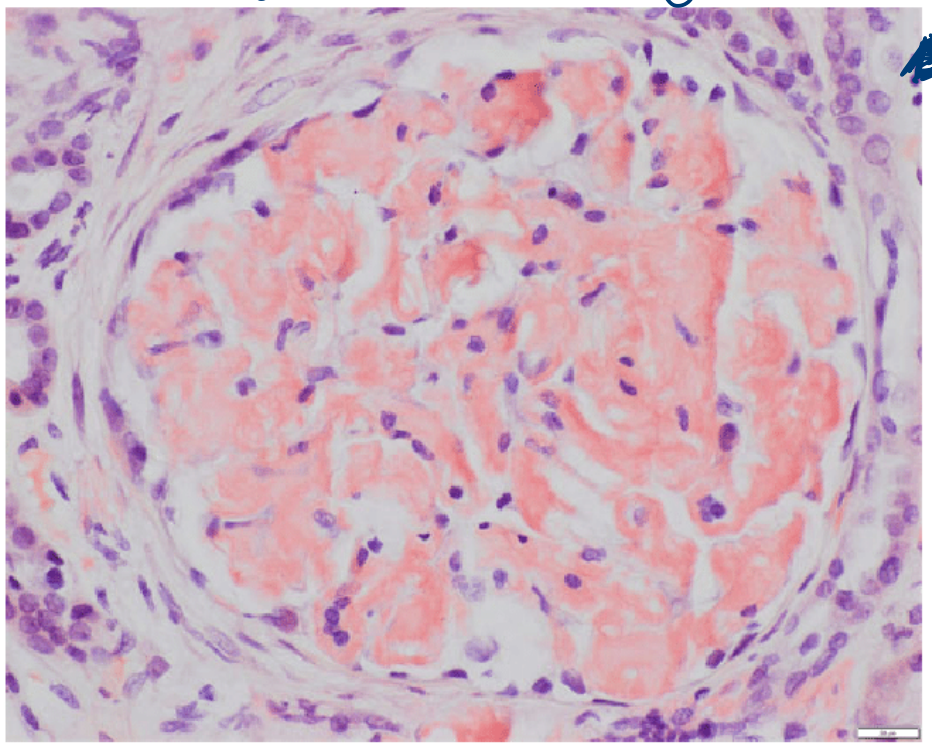
peripheral neuropathy
- length dependant polyneuropathy

Bilateral carpal tunnel.

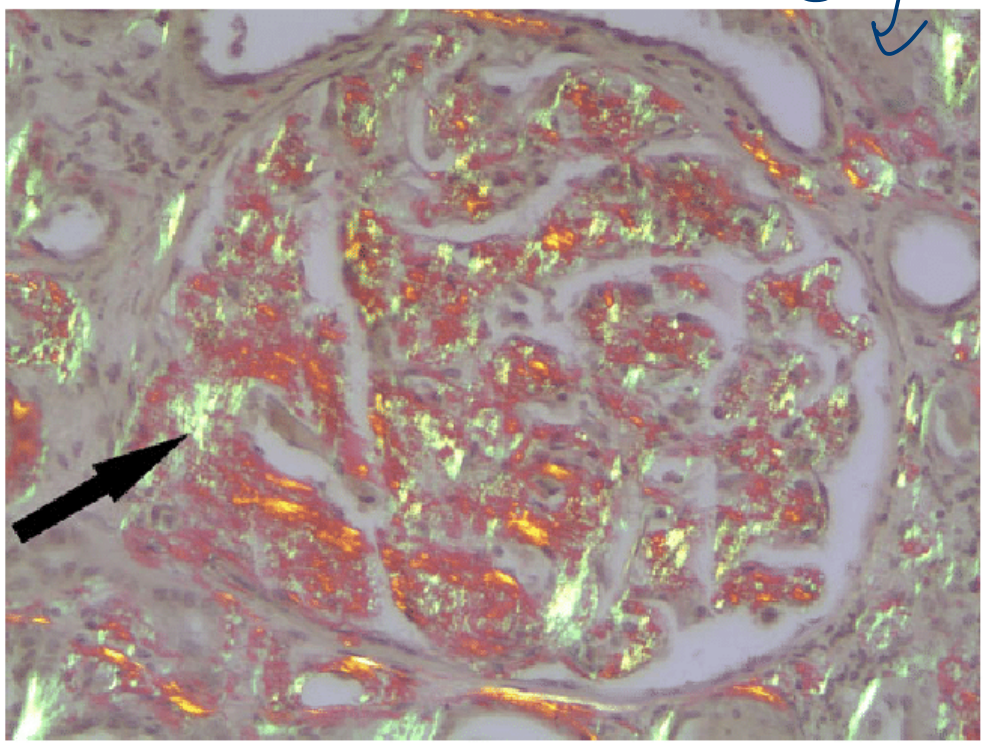


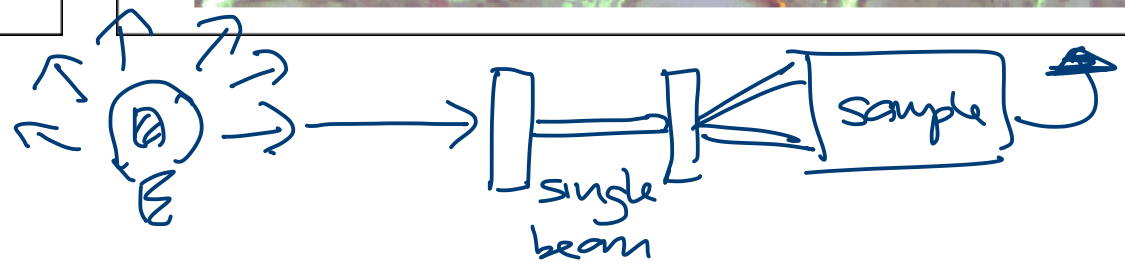
- ↓ GFR
- proteinuria severe
  → nephrotic range >3g/day

Light Micro: congo red (+)



Polarized Light Microscopy





MCQ

Which of the following is the most common cause of systemic amyloidosis in developed nations?

A. AL amyloidosis
B. AA amyloidosis
C. ATTR wild type amyloidosis
D. ATTR variant (hereditary) amyloidosis
E. B2M amyloidosis

AL Amyloidosis

MGUS essential — not nec myeloma

clonal population.

plasma cell or B cell.

⇒ light chains κ/λ. ⇒ lots same.

x lots.

monoclonal protein.

⇒ same ⇒ prone to misfolding ⇒ amyloid.

What tests will you perform in **EVERY** suspected amyloid case?

SPEP. | SFLC

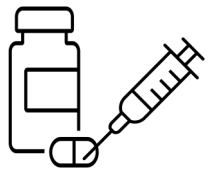
If you don't have MGUS
You don't have AL amyloid

BUT… MGUS ≠ amyloid.

…where might you source tissue?

⇒ BMAT
⇒ Fat pad (abdo)
⇒ organ.

if diagnosis AL amyloid,

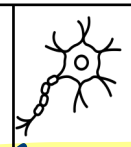


kill the clone

- chemo
- autoHSCT.

() very similar to myeloma.

Common Organs Affected

Precursor	Amyloid				Other
light chains	AL.	✓	✓	✓	
-					

assess organ. function

Specific signs that may be seen in 15% of patients:

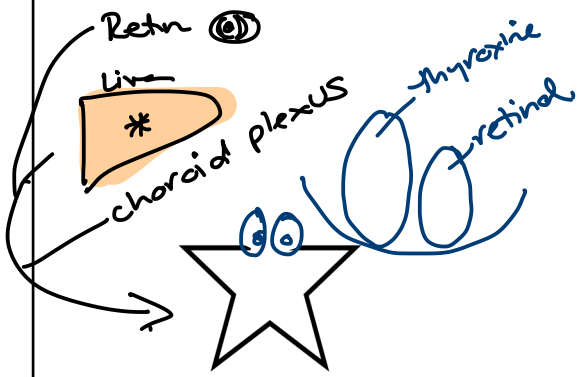
macroglossia.

purpura eyelids

ATTR Amyloidosis

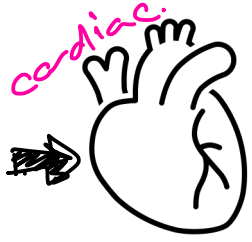
Bilateral carpal tunnel syndrome, tendinopathy, or lumbar canal stenosis may precede other manifestations by 5-15 years

The NUMBER TWO most common cause of systemic amyloid



TTR gene.

'senile' / ageing.
wild type.
ATTRwt

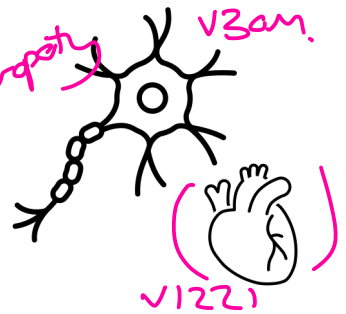


old men.
90% men.
> 66yr.

& This is THE most common cause of cardiac amyloid

hereditary variant.
ATTRv

Aut Dominant.
⇒ ♀ / ♂
⇒ 3rd-5th decade.



Diagnostic Approach
Cardiac Amyloid Suspected

What tests will you perform in EVERY suspected amyloid case?

SPEP
SFLC.
target monoclonal.

No MGUS

Bone Scan.

MGUS +

haem workup.
⇒ tissue.
⇒

Treatments

STABILISERS – Tafamadis
wild type/ cardiac ATTR
→ keep tetramer form
Diflunisal.

SILENCERS – Patisiran, Inotersen.
→ ↓ expression of TTR in liver.
⇒ Bind to mRNA.
genetic.

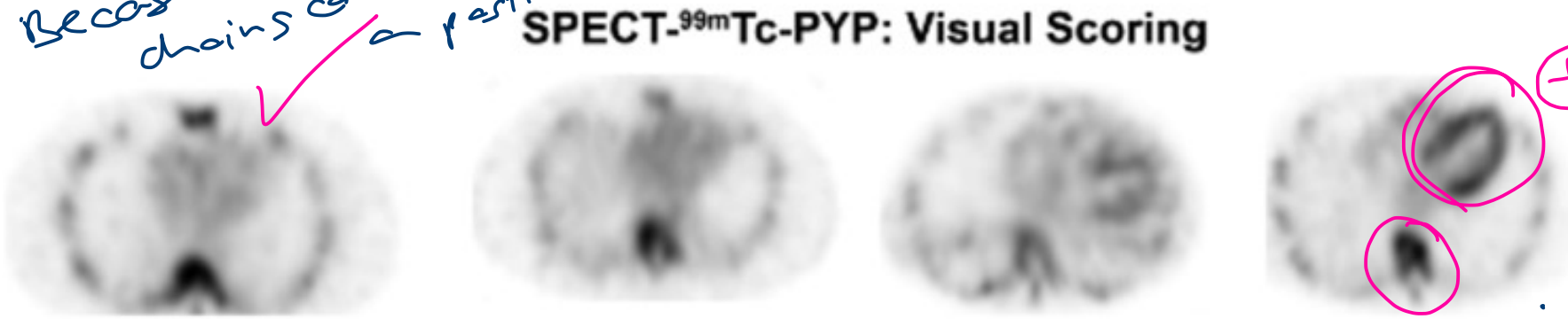
wt./v. Amyloidosis

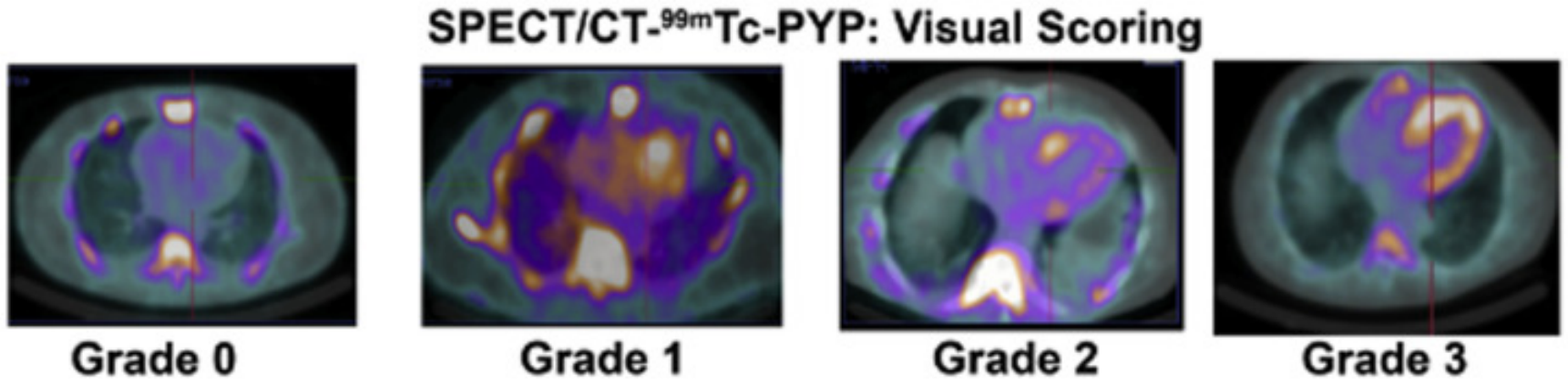
genetic testing
– treatment option.
– family members

If you diagnose ATTR amyloid

– Bone Scintigraphy in ATTR cardiac amyloidosis

This only helpful if MGUS ⊖ Because light chains can also cause a positive scan.





https://www.sciencedirect.com/science/article/pii/S0735109720349329#fig1

MCQ

A 65 year old man with a history of bilateral carpal tunnel syndrome presents with dyspnoea on exertion. Cardiac stress testing reveals no evidence of inducible ischaemia. His blood pressure is 130/80 and he is on no regular medications. An echocardiogram shows increased LV wall thickness and longitudinal strain pattern with apical sparing. You suspect amyloidosis. Serum protein electrophoresis is negative.

Which test would you now perform to explore the cause of amyloidosis in this gentleman?

A. Bone scintigraphy
B. Cardiac MRI
C. Cardiac biopsy
D. Renal biopsy
E. Bone Marrow Aspirate

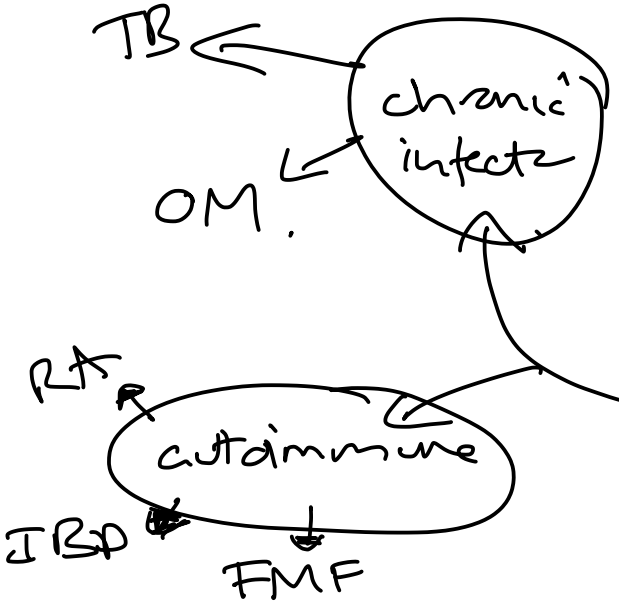
MCQ

A 65 year old man with longstanding rheumatoid arthritis and active synovitis is found to have renal impairment and proteinuria 3.9g/day. Serum protein electrophoresis is negative. A renal biopsy is positive for congo red staining. Immune stains are negative.

Which of the following proteins may lead to AA amyloidosis?

A. Serum Amyloid A
B. Transthyretin
C. B2 microglobulin
D. Kappa light chain
E. Lambda light chain

AA amyloidosis



serum amyloid A.

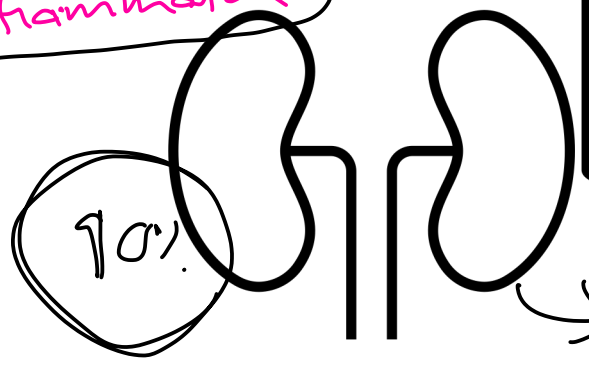
↳ acute phase reactant.

↓.

genetic / environmental.

chronic inflammatory

IL-1
IL6
TNFα



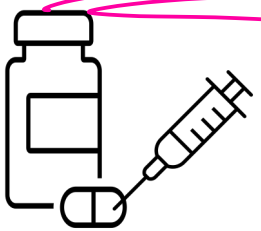
90%.

Biopsy

AAAAAAA!
My favourite organ!

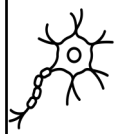
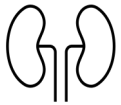
- ↓GFR
- nephrotic range proteinuria
  ≥3g/day.

Treatment



TREAT CAUSE

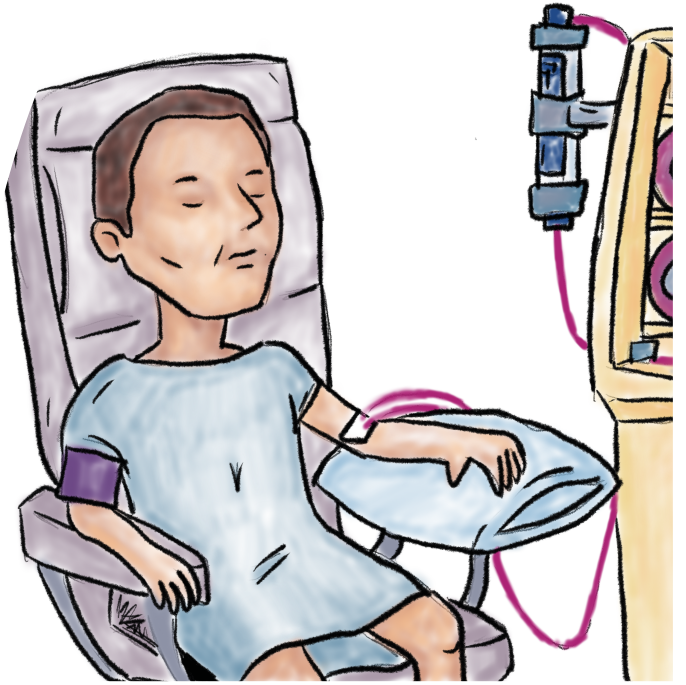
Common Organs Affected

Precursor	Amyloid				Other
serum amyloid A	AA	✗	✗	✓	GI 30%. treat

MCQ

With modern dialysis techniques which of the following is the strongest risk factor for developing dialysis associated amyloidosis

A. Number of years on dialysis
B. Peritoneal Dialysis
C. Chronic Inflammation
D. Low Residual Renal Function
E. Synthetic haemodialysis membranes



B2M Amyloidosis

B2microglobulin.

↳ processed in kidneys

↳ ESRF ⇒ build up

MSK.

pathological fractures

Possible Presentations

Carpal Tunnel

Bilateral shoulder pain

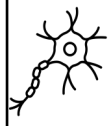
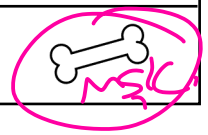
Flexor Tenosynovitis

Neck pain (Destructive Spondylarthropathy)

Radiological: Bone Cysts

Rx: optimise dialysis
transplant.
analgesia / ortho

Common Organs Affected

Precursor	Amyloid				Other
B2microglobulin.	Aβ2M.	X	X	X	 MSK

Mostly Deposits MSK
Less so blood vessels & GI tract

KEY RISK FACTORS:

longer dialysis vintage

increasing age,

low flux dialyser,

lack of residual function

PD removes B2M less well but PD patients have better residual function