CheckRare

Rare and Genetic Disease Network

CME

TTR Amyloidosis

What Clinicians Need to Know About Its Pathophysiology

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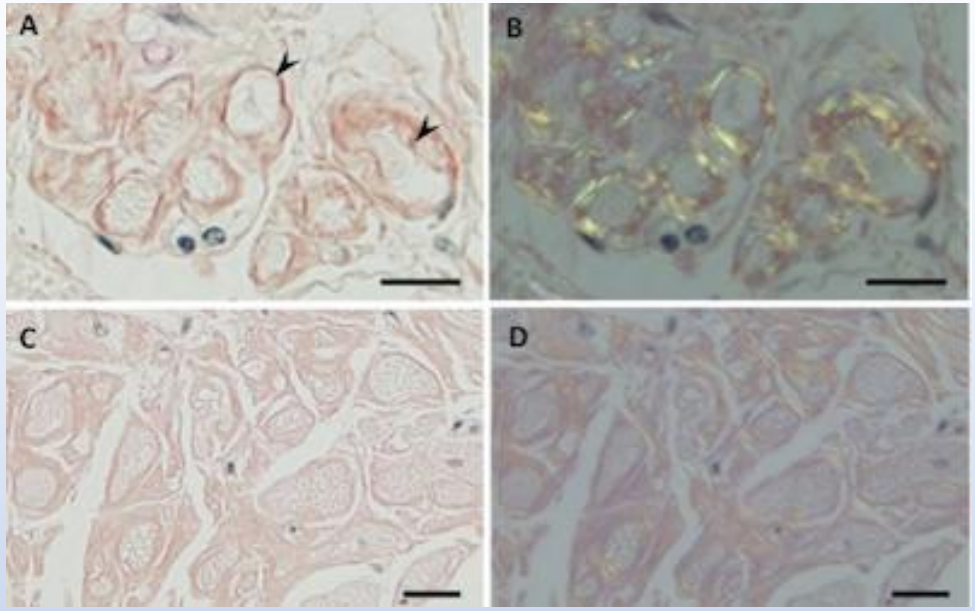
Pathophysiology

What Is Amyloidosis?

- Heterogeneous group of disorders
- Deposit of amyloid that disrupt normal tissue structure and function
- 30+ proteins associated with amyloidosis [including transthyretin (TTR)]

What Is TTR?

- Synthesized in the liver
- Transports thyroxine and retinol
- Mutations in *TTR* gene form insoluble amyloid fibrils



Cardiac amyloid deposits in early-onset ATTR Val30Met amyloidosis patients from endemic foci (**A**,**B**) and late-onset ATTR Val30Met amyloidosis from nonendemic areas (**C**,**D**). Alkaline Congo red staining.

Koike H, Katsuna M. *Biomedicines* 2019.

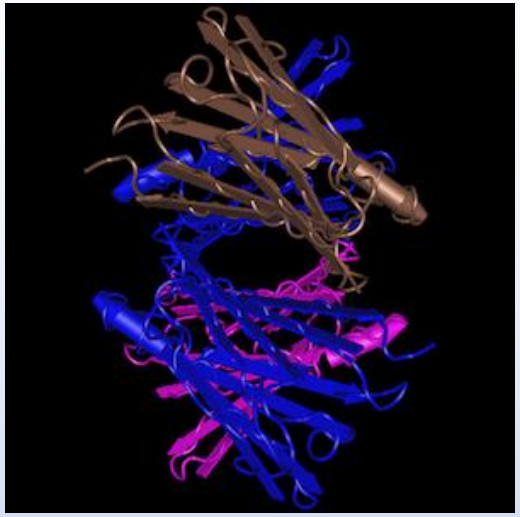
TTR Mutations

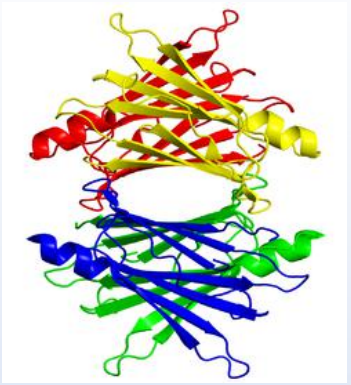
TTR Mutations

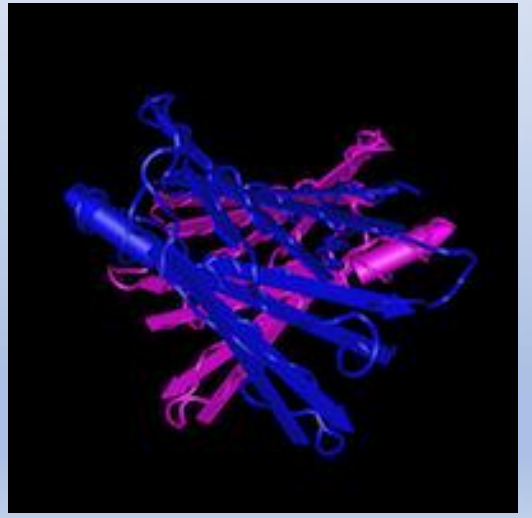
- 120 mutations identified
- In the US - Val122Ile, Thr60Ala, Val30Met
- Globally - Val30Met, Val122Ile, Glu89Gln

Mutations and Symptoms

- Val30Met (top left) - polyneuropathy
- Val122Ile (bottom right) - cardiopathy
- High variance among the patient population







Multiple Systems Impacted

Nervous System

- Progressive dementia
- Headache
- Ataxia
- Seizures
- Stroke-like episodes
- Spastic paresis
- Orthostatic hypotension
- Sexual dysfunction

Neuromuscular

- Muscle weakness
- Neuropathic pain
- Difficulty walking

Ocular

- Vitreous opacification
- Glaucoma
- Papillary abnormalities

Cardiovascular

- Conduction blocks
- Cardiomyopathy
- Arrhythmia

Gastrointestinal

- Nausea / vomiting
- Early satiety
- Diarrhea and/or constipation

Renal

- Proteinuria
- Renal failure

FAP vs FAC vs WT

	Familial Amyloid Polyneuropathy (FAP)	Familial Amyloid Cardiomyopathy (FAC)	Wild type - Senile Systemic Amyloidosis (WT)
Primary symptoms	Sensory motor neuropathy	Restrictive cardiomyopathy	Restrictive cardiomyopathy
Common mutation	V30M (50% world-wide)	V122I (4% African Americans)	Wild-type
Cause of death	Cachexia, renal failure, cardiac disease, sudden death	Heart failure	Heart failure
Patients worldwide	~10,000	~40,000	Unknown (Deposits in ~25% autopsies)
Age on onset	30-50 years	60-70 years	>70 yrs; mostly men
Life expectancy after diagnosis	~5-15 years	~3-5 years	~3-5 years

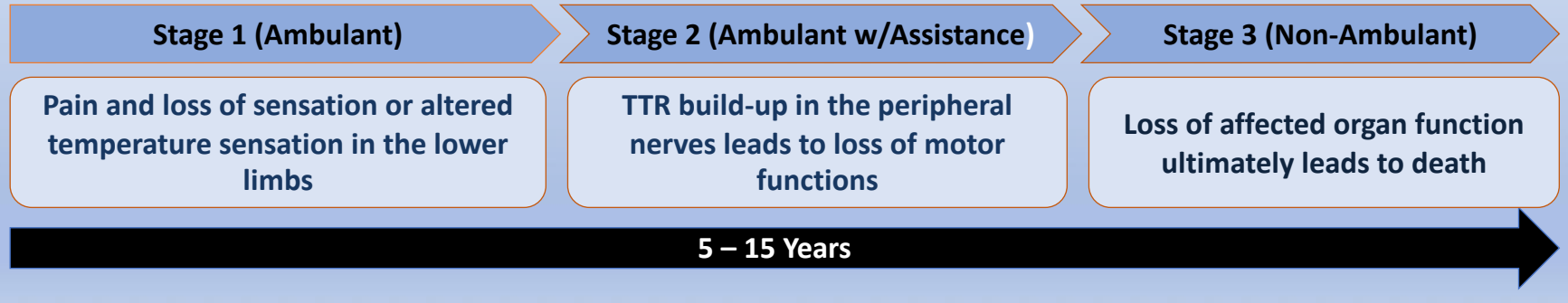
How to clinic research al trials?

FAP

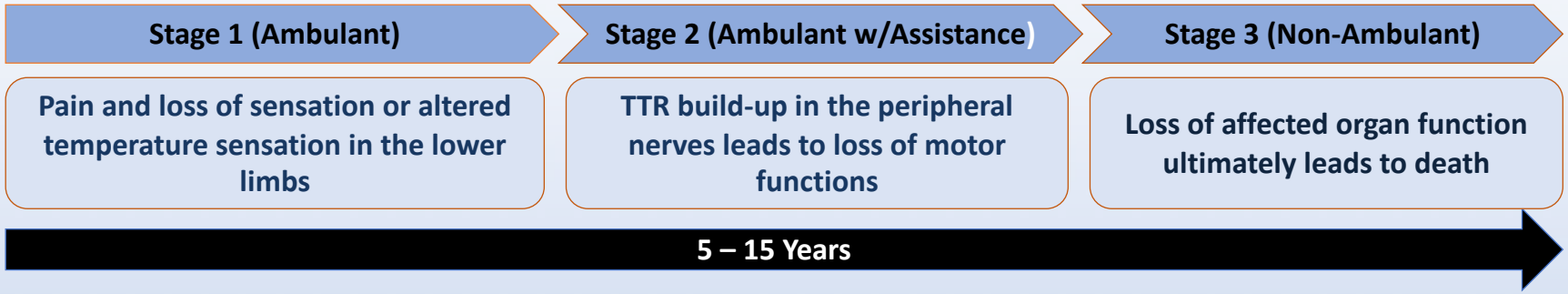
Primarily affects the peripheral nervous system, but often effects the heart, kidneys and eyes.

- **Fatal genetic disease:**
  - Patients face a relentless progression to death (within 5-15 years of onset) with limited treatment options
- **Painful:**
  - Nerve damage causes severe pain, limb weakness, loss of sensation, disturbance of bowel/bladder and sexual dysfunction
- **Multi-organ failure:**
  - Heart, kidneys and peripheral nerves

- **Stages of FAP:**



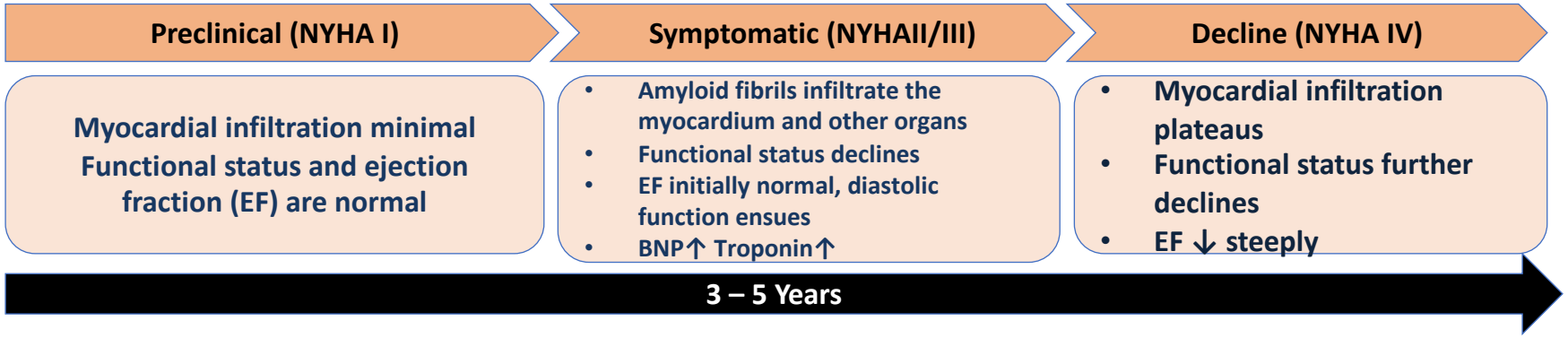
FAP


Stage 1 (Ambulant)
Stage 2 (Ambulant w/Assistance)
Stage 3 (Non-Ambulant)
Pain and loss of sensation or altered temperature sensation in the lower limbs
TTR build-up in the peripheral nerves leads to loss of motor functions
Loss of affected organ function ultimately leads to death
5 – 15 Years

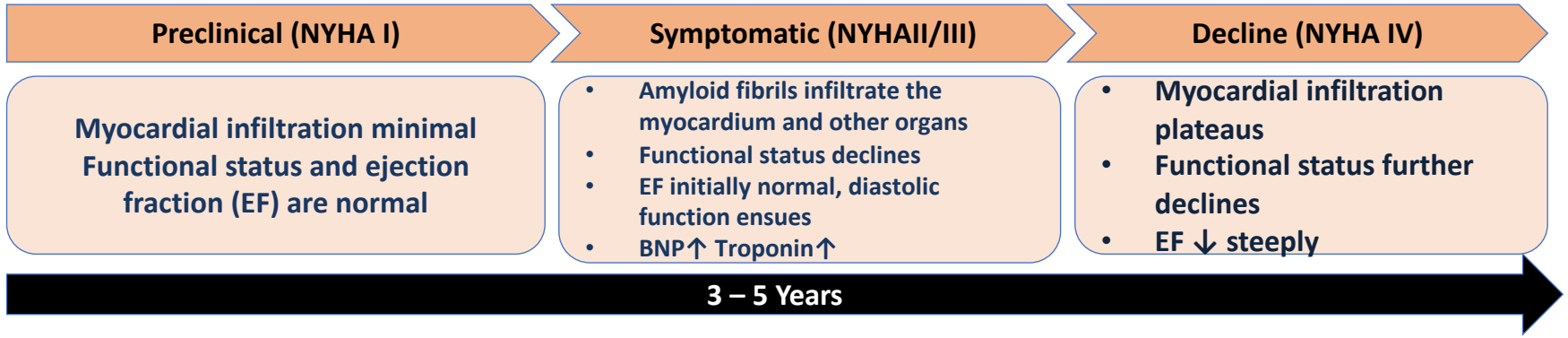
FAC and WT

Amyloid infiltrates the heart leading to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure

- **Symptoms:**
  - Shortness of breath, palpitations and abnormal heart rhythms, fluid retention in legs, weight loss, nausea, fatigue, dizziness and collapse, disrupted sleep and angina
- **Frequent hospitalizations** for congestive heart failure in late stages of disease
- **Death** in <5 years



FAC and WT


Preclinical (NYHA I)
Symptomatic (NYHAII/III)
Decline (NYHA IV)
Myocardial infiltration minimal
Functional status and ejection fraction (EF) are normal
Amyloid fibrils infiltrate the myocardium and other organs
Functional status declines
EF initially normal, diastolic function ensues
BNP↑ Troponin↑
Myocardial infiltration plateaus
Functional status further declines
EF ↓ steeply
3 – 5 Years

Treatment Options

- **Symptom relief**
- **Liver transplantation**
- **TTR stabilizers**
  - Tafamidis
  - Diflunisal
- **TTR production blockers**
  - Inotersen
  - Patisiran