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Rare and Genetic Disease Network

# CME / CE

# Diagnosing ATTR Amyloidosis

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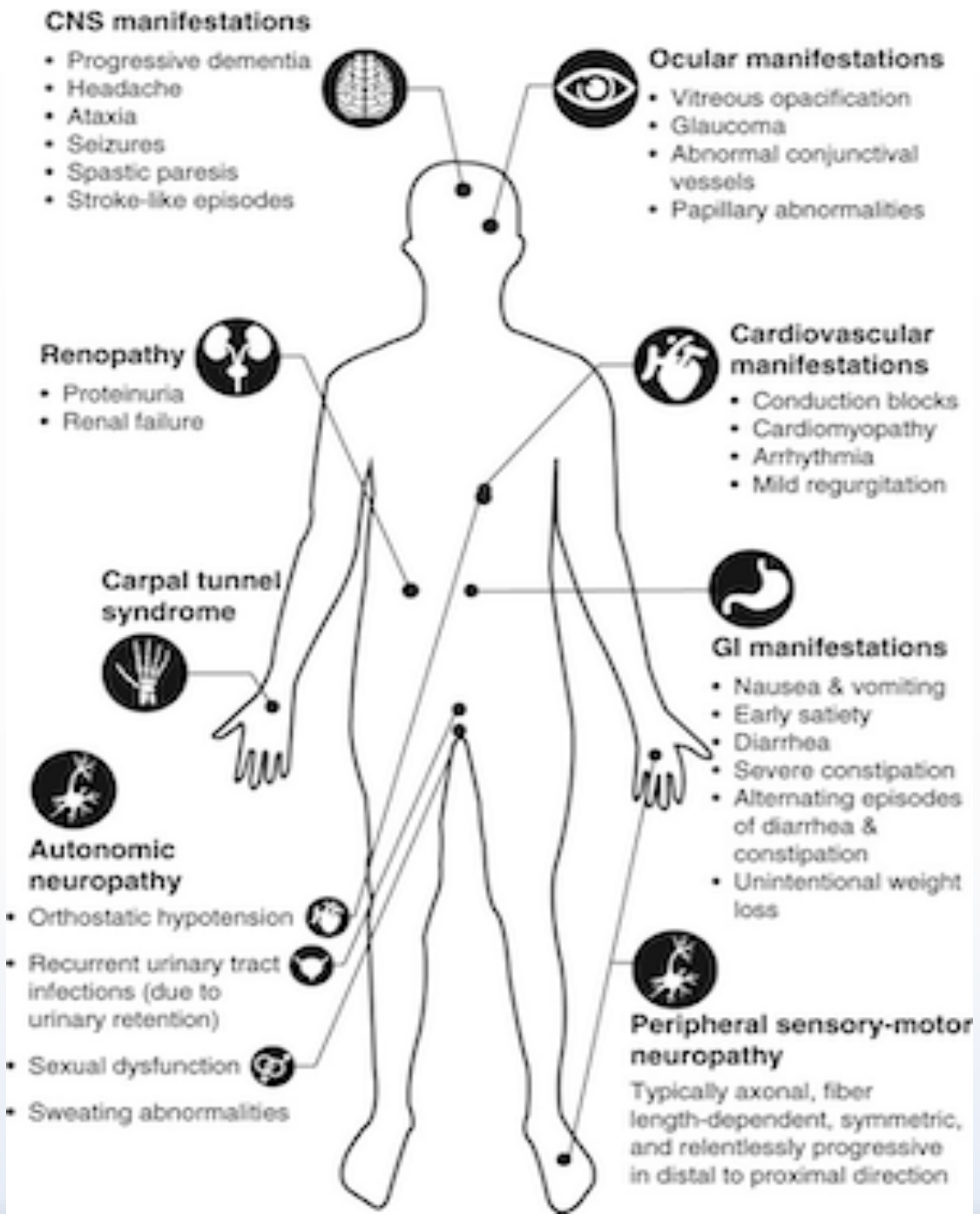
# When to Suspect TTR Amyloidosis

**Family History**

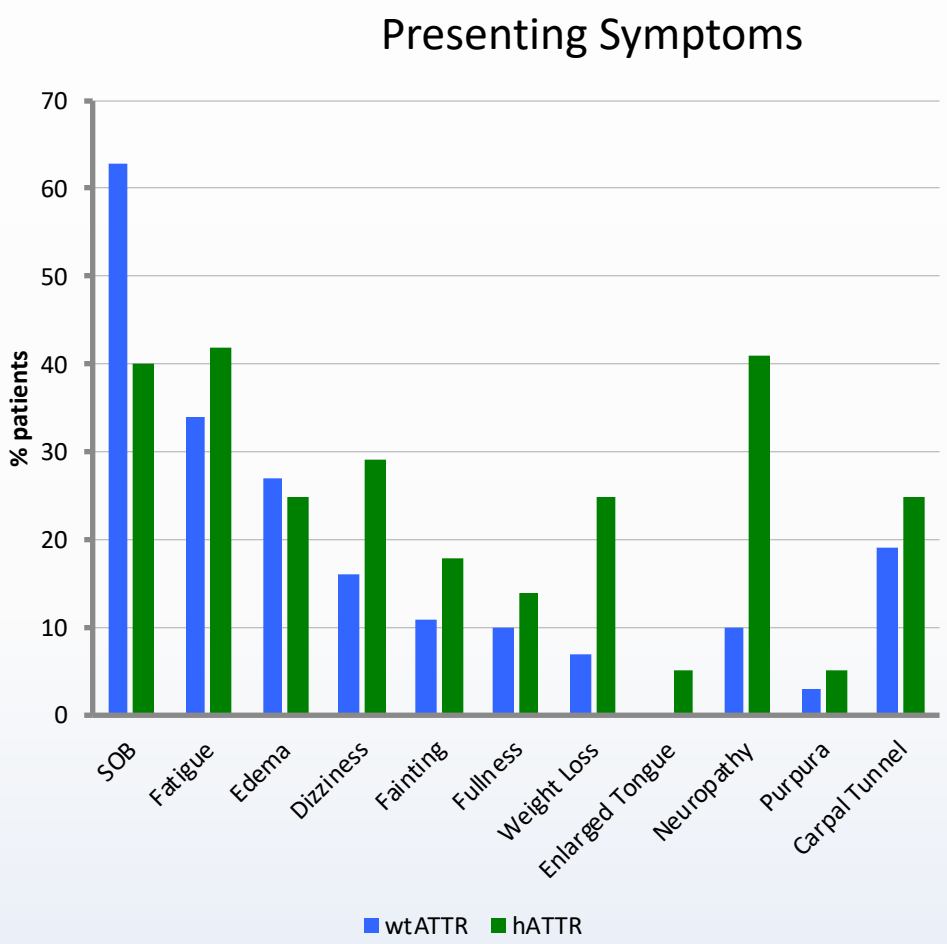
**Carpal Tunnel**

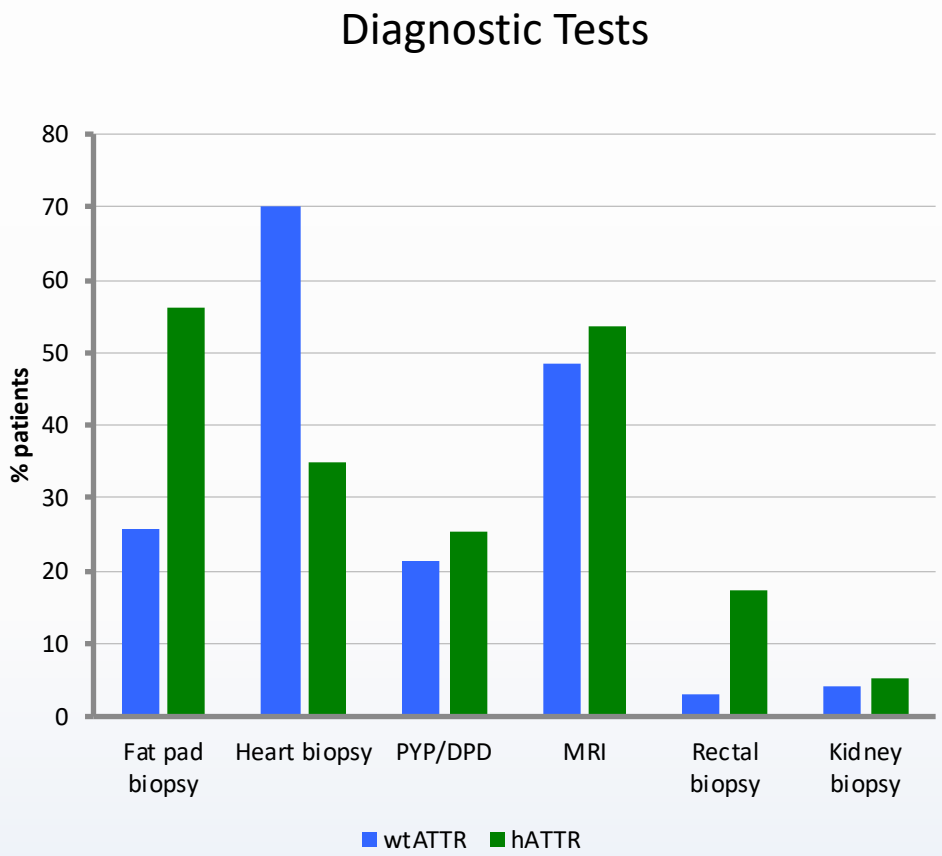
**Cardiomyopathies**




Conceição et al. *J Peripher Nerv Syst.* 2016;21(1):5-9.

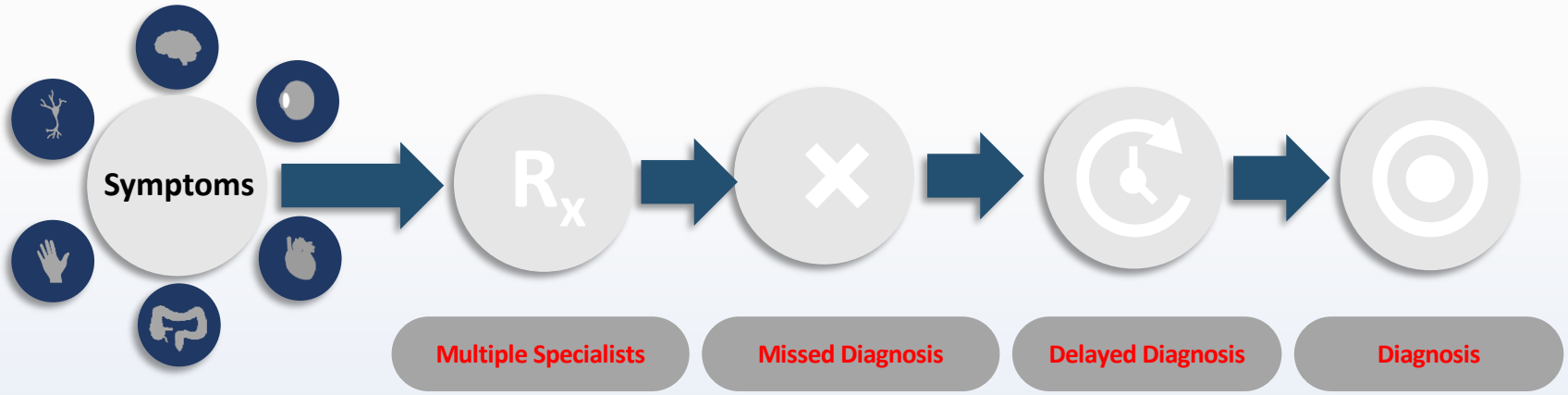
# Symptoms and Diagnostic Tests



# Diagnostic Delays Common

- Time to diagnosis, 2-3 years (regardless of family history)[1]
- In a single study, diagnosis took >6 years after the onset of symptoms for 1 in 10 patients[1]
  - For hATTR with polyneuropathy, mean time to diagnosis is 4 years (range, 1-10)[2]
- 45% of hATTR patients report initial misdiagnosis
  - Common misdiagnoses include carpal tunnel syndrome, idiopathic polyneuropathy, ocular herpes, Sjogren's Syndrome, IBS, bronchitis, congestive heart failure, GERD, spinal problems, gastroparesis, COPD, NSAID-induced constipation, plantar fasciitis, and / or fibromyalgia
  - Patients with hATTR amyloidosis may inappropriately receive chemotherapy if AL amyloidosis is suspected[3]



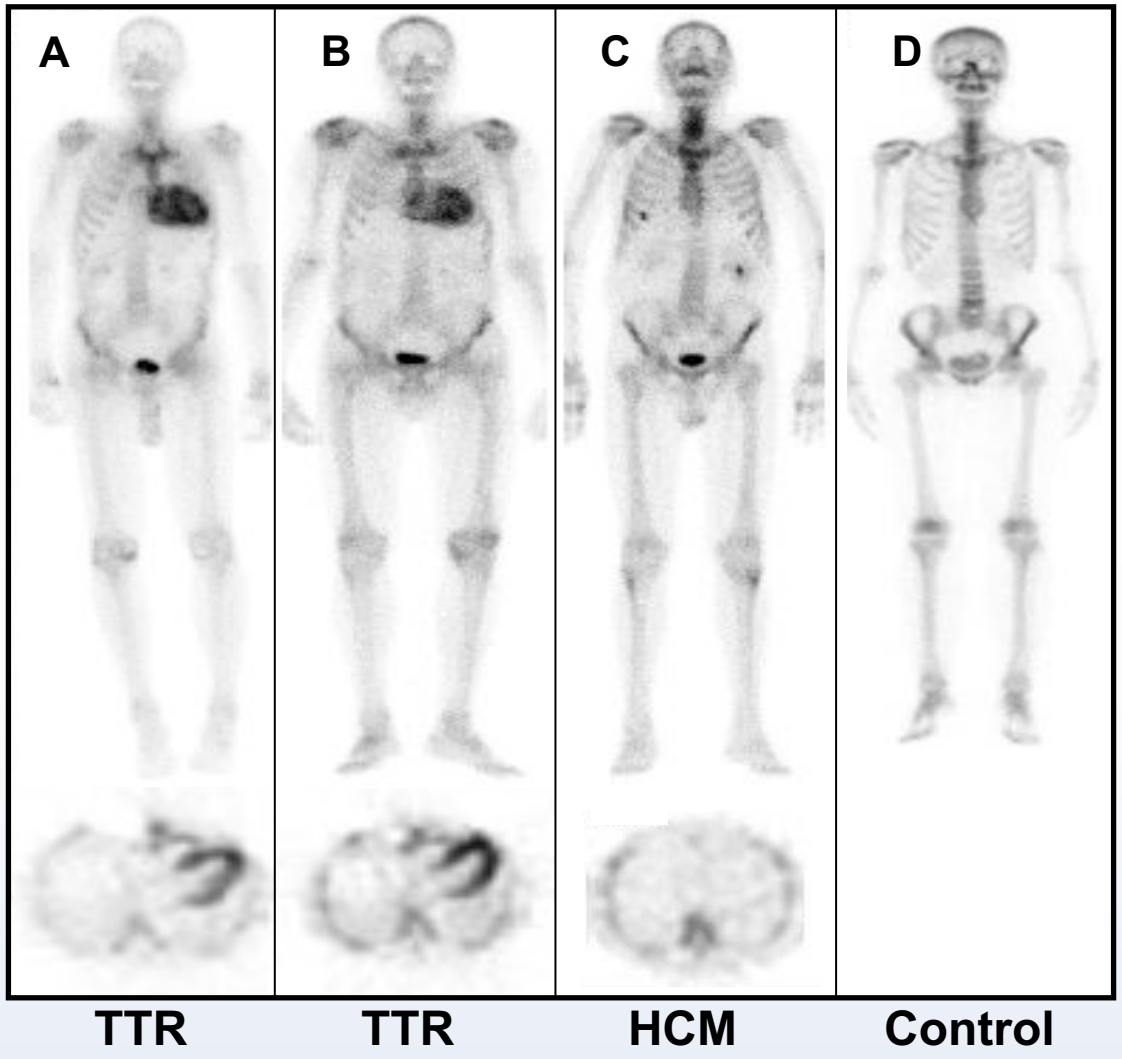

1. Amyloidosis Foundation. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis);
2. 2. Plante-Bordeneuve V. *Neurology*. 2007; 69(7):693-8; 3. Lachmann H et al. *NEJM* 2002 1786-91.

# Diagnosis

- **Tissue biopsy is required for histologic confirmation[1-3]**
  - Common tissues biopsied include subcutaneous fatty tissue of the abdominal wall, kidney, skin, gastric, or rectal mucosa, sural nerve tissue, retinaculum and peritendinous fat obtained at carpal tunnel surgery, tissue from the salivary gland, and endomyocardial tissue (for cardiac amyloidosis)
- **Congo red staining of amyloid is the gold standard for diagnosis[1,2]**
- **A diagnostic algorithm proposed by Gillmore et al. based on myocardial radiotracer uptake on bone scintigraphy has been developed for use in patients with cardiac ATTR amyloidosis[4]**
  - Use of myocardial radiotracer uptake on bone scintigraphy may also eliminate the need for biopsy in patients with cardiac ATTR amyloidosis
- **Amyloid typing may be achieved using a variety of techniques[1,2]**
  - Immunohistochemistry and immunofluorescence
  - Proteomics can be utilized for amyloidosis typing
  - Mass spectrometry
- **Laser microdissection and mass spectrometry is the gold-standard for amyloid typing[2]**
- **Genetic testing is recommended for confirmation and detection of specific TTR gene mutations[1,2]**

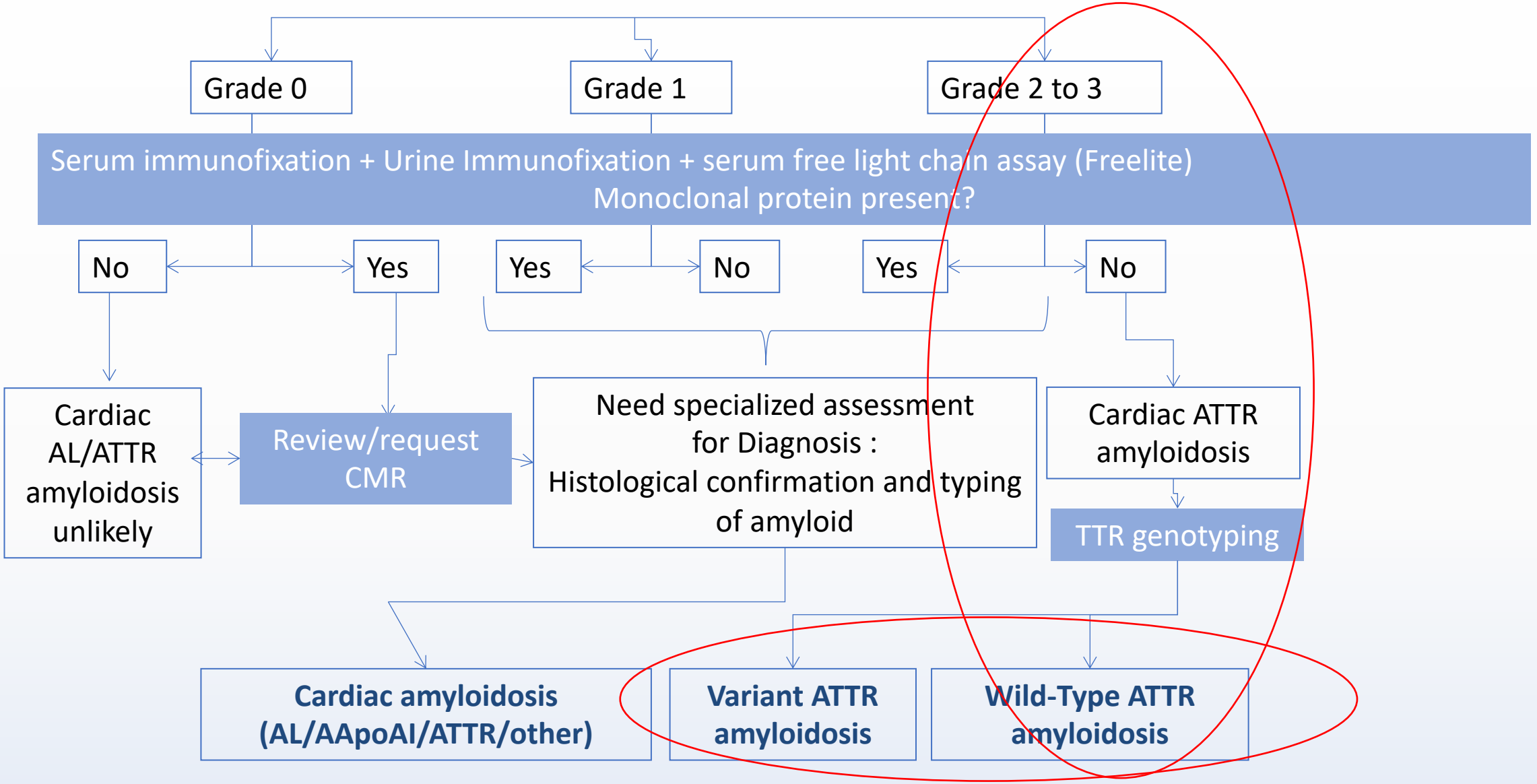
1. Ando Y et al. *Orphanet Journal of Rare Diseases 2013, 8:31; 2.* Leung N, Nasr S, and Sethi S. *Blood* 2012;120:3206-3213;
3. Castaño A et al. *J Nucl Cardiol* 2016;23:1355-1363. 4. Gillmore JD et al. *Circulation* 2016; 133: 2404-12

# Bone scintigraphy with $^{99m}$Tc-DPD/HMDP/PYP




Quarta CC et al JACC Cv Img 2012; 5: 755-8.

# Bone scintigraphy with $^{99m}$Tc-DPD/HMDP/PYP



# Diagnostic Tools

| | ECHO | MRI | Scintigraphy | BNP | Other |
|---|---|---|---|---|---|
| **Suspicion** | +++ | ++ | + (TTR) | + | |
| **Definite diagnosis** | + | ++ | +++ (TTR) | - | |
| **Etiologic diagnosis** | +/- | +? | +++ | +/- | RBP4 |
| **Early diagnosis** | + | ? | ++ (TTR) | +/? | |
| **Functional eval** | +++ | ++ | + (MIBG) | - | |
| **Prognosis** | + | ++ | + | +++ | 6MWT |
| **Amyloiditic burden** | + | ++ | +? | - | |
| **Response to Tx** | + | + | ? | +++? | 6MWT? |

Table provided by Dr. Gertz

# Patient 1

- 68-yr-old male
- Progressive lower extremity numbness – “I feel like I’m walking on thick pile carpeting.”
- Neurology - EMG confirms mixed axonal demyelinating neuropathy
- Screens for diabetes and heavy metals negative
- Observed 1 year paresthesia ascending to calf
- Skin biopsy performed, shows amyloidosis
- Referred to hematology

# Patient 1

- Given a trial of lenalidomide and dexamethasone - no benefit
- Develops diarrhea and orthostatic hypotension
- Another year elapses Weight loss 8 kg
- Second opinion skin biopsy analyzed by LC-MS and amyloid deposits sequenced as TTR
- Genetic studies reveal V50M TTR mutation

# Patient 2

- 58-yr-old male
- Bilateral CTS 6 years earlier
- Impotence 3 years  earlier
- Comes for evaluation for low lower extremity numbness and swelling
- EMG confirmed axonal and demyelinating neuropathy
- Edema treated with furosemide 20 milligrams daily

# Patient 2

- Small monoclonal IgG kappa protein found in serum 0.3 g/dl
- Patient is diagnosed as DADS (Distal acquired demyelinating symmetric  neuropathy)/CIDP
- Placed on a course of plasma exchange for 3 months
- Neuropathy worsens
- Patient begins intravenous immunoglobulin infusions 1 year – neuropathy worsens

# Patient 2

- Patient goes to cardiologist because the lower extremity edema worsens on diuretics and he begins to develop dyspnea on exertion
- Echocardiogram performed and it is consistent with infiltrative cardiomyopathy–amyloid
- Patient undergoes pyrophosphate scanning which is strongly positive for TTR amyloidosis
- Genetic testing reveals **Ser97Tyr**
- Subsequent family history reveals father died of heart failure and had difficulty walking the last 2 years of his life

# Clinical Pearls

- ATTR amyloidosis is the great pretender
- Diagnostic delays very common
- Early suspicion can lead to early diagnosis and treatment
- Diagnostic tools such as bone scintigraphy key to diagnosis
- With treatment, this disease is no longer a death sentence

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