Variable Presentation and Pathologic Overlap of Rare Neuromuscular Condition

Shailesh Reddy MD, PGY-3 Physical Medicine and Rehabilitation [2]

Yessar Hussain MD, Neuromuscular Medicine [1]

Christina Paul MD, PGY-2 Physical Medicine and Rehabilitation [3]

The University of Texas at Austin
Dell Medical School

Austin Neuromuscular Center

Patient Case #1

- 58 year old man presented with progressive proximal lower extremities weakness over 2 years with minimal hands weakness, with numbness and tingling and burning pain at his feet.
- He noted Quads atrophy and mild ankle swelling.
- He denies dysphagia, SOB, postural lightheadedness and GI symptoms.
- He was referred for evaluation of possible CIDP.
- PMHx: ankle edema.
- SHx: Former smoker, social etoh.
- FHx: non contributory.

Physical Exam

- Quantitative muscle test (Right/Left): Deltoid: 30/30 Biceps: 30/30 Grip: 55/45 IP: 27/18 Quads: 33/13 TA: 28/20
- Quadriceps atrophy noted bilaterally
- Reflexes: trace from LUs, 1+ from UEs.
- Sensory: QVT: Knees: 6/8 Toes: 4/8, with normal joint position.
- Gait: wide based, trouble in getting from setting position.
- FVC 3.4 L at supine and sitting.
- His prior extensive work up non diagnostic, with normal CK.

Electrodiagnostic Study

-Symmetrical sensorimotor axonal neuropathy with secondary demyelinating changes

-Proximal myopathic changes

SNC

Nerve / Sites	Rec. Site	Onset Lat ms	Peak Lat ms	Amp µV	Segments	Distance mm	Velocity m/s
R Median - Digit II (Antidromic)							
Wrist	Dig II	NR	NR	NR	Wrist - Dig II	140	NR
L Median - Digit II (Antidromic)							
Wrist	Dig II	NR	NR	NR	Wrist - Dig II	140	NR
L Ulnar - Digit V (Antidromic)							
Wrist	Dig V	3.13	3.65	3.2	Wrist - Dig V	140	45
R Radial - Anatomical snuff box (Forearm)							
Forearm	Wrist	NR	NR	NR	Forearm - Wrist	100	NR
R Sural - Ankle (Calf)							
Calf	Ankle	NR	NR	NR	Calf - Ankle	140	NR

MNC

Nerve / Sites	Muscle	Latency ms	Amplitude mV	Duration ms	Rel Amp %	Segments	Distance mm	Lat Diff ms	Velocity m/s
R Median - APB									
Wrist	APB	5.63	2.2	7.14	100	Wrist - APB	70		
Elbow	APB	10.05	1.5	7.45	66.4	Elbow - Wrist	235	4.43	53
L Median - APB									
Wrist	APB	4.58	2.1	8.18	100	Wrist - APB	70		
Elbow	APB	8.96	1.8	8.18	83	Elbow - Wrist	210	4.38	48
Upper arm	APB	11.98	1.5	8.07	88.1	Upper arm - Elbow	150	3.02	50
R Ulnar - ADM									
Wrist	ADM	3.44	6.2	7.40	100	Wrist - ADM	70		
B.Elbow	ADM	6.72	5.6	7.45	91.4	B.Elbow - Wrist	170	3.28	52
A.Elbow	ADM	9.06	5.8	7.34	102	A.Elbow - B.Elbow	100	2.34	43
						A.Elbow - Wrist		5.63	
L Ulnar - ADM									
Wrist	ADM	3.02	4.4	6.93	100	Wrist - ADM	70		
B.Elbow	ADM	7.14	4.5	7.03	102	B.Elbow - Wrist	190	4.11	46
A.Elbow	ADM	10.05	4.3	7.34	95.2	A.Elbow - B.Elbow	100	2.92	34
Axilla	ADM	11.82	4.3	7.40	99	Axilla - A.Elbow	100	1.77	56
						A.Elbow - Wrist		7.03	
R Peroneal - EDB									
Ankle	EDB	5.94	0.5	4.90	100	Ankle - EDB	100		
Fib head	EDB	12.24	0.3	4.43	72.5	Fib head - Ankle	265	6.30	42
						Pop fossa - Ankle			
R Tibial - AH									
Ankle	AH	5.68	0.3	7.86	100	Ankle - AH	100		
Pop fossa	AH	13.33	0.0	9.74	8.74	Pop fossa - Ankle	340	7.66	44

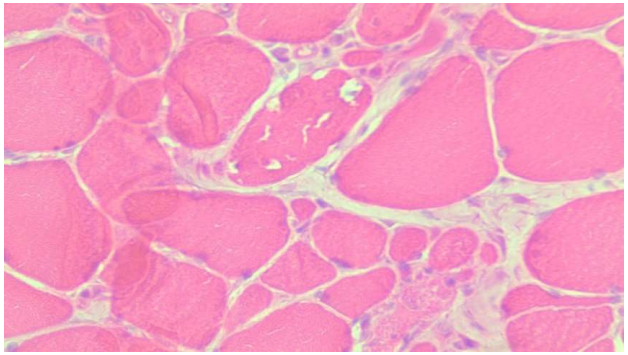
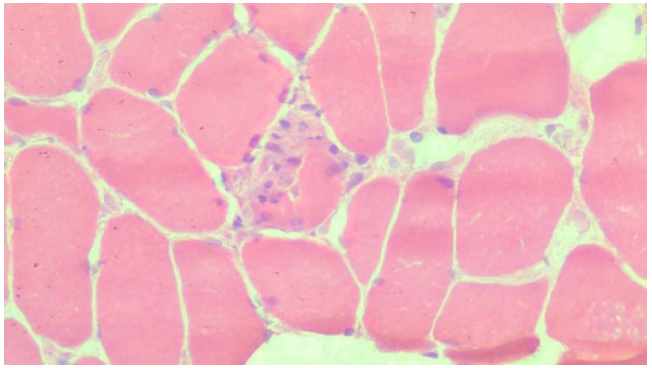
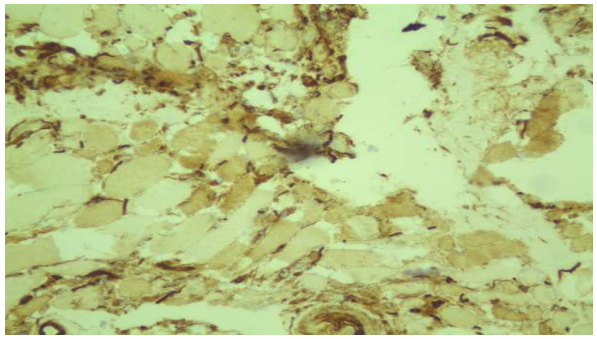
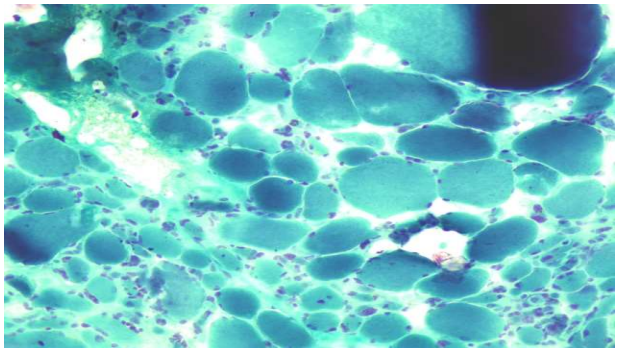
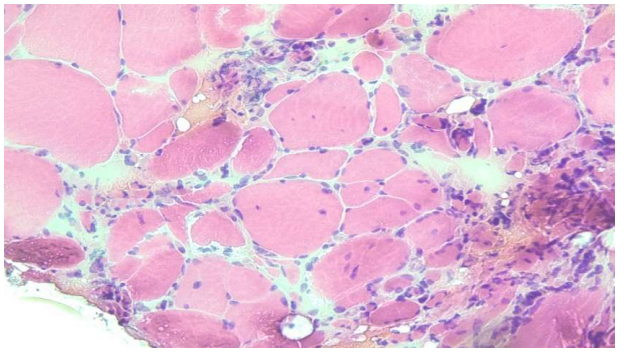
F Wave

Nerve	F Lat ms	M Lat ms	F-M Lat ms
R Ulnar - ADM	33.7	4.0	29.7
L Median - APB	31.1	4.9	26.3

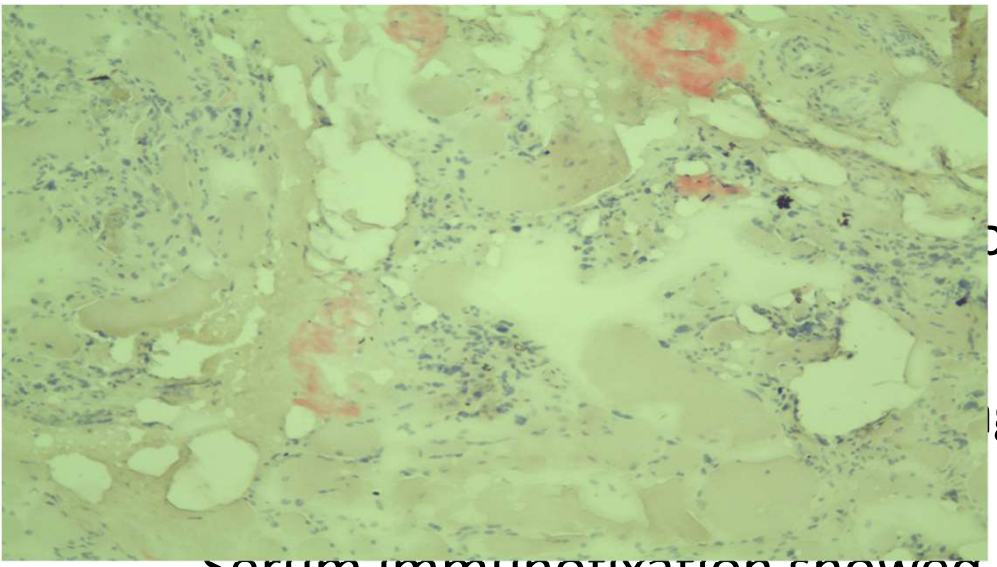
Our Differential Diagnosis Of Mixed Neuropathy and Myopathy

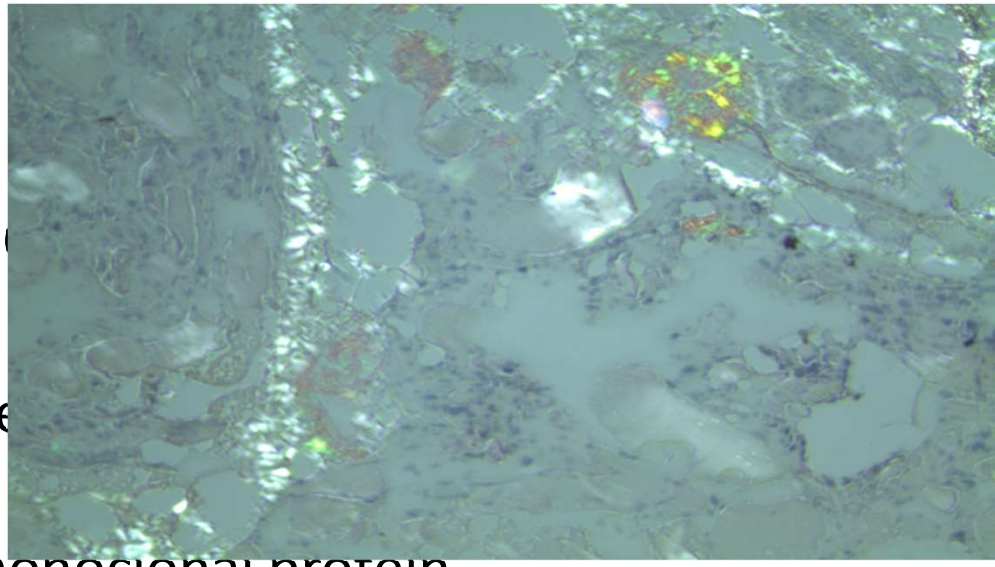
- Sarcoidosis
- HIV
- Amyloidosis
- IBM
- etc,,

Muscle pathology

- Chronic and active myopathic change with CD3/4 infiltration, and rare basophilic rimmed vacuoles present





on Bo

gnose

- Serum immunofixation showed no monoclonal protein.
- Further muscle staining showed amyloid with Congo Red.

- Positive TTR-*Ser97* mutation

The University of Texas at Austin
Dell Medical School

Austin Neuromuscular Center

Patient #2

- 75 year old male presented with 9 year history of paresthesias ascending in both hands and feet and proximal and distal weakness. Was diagnosed with CIDP, supported by EMG/NCS and treated with IVIG and plasmapheresis for 2 years. Despite this he continued to deteriorate and developed muscle weakness and atrophy. Functionally he went from using a cane to using a wheelchair.
- During his treatment course he started developed SOB and ankle edema and was diagnosed with CHF.
- Noted to have 2 siblings died from heart failure.
- Further work up:
  - Nerve biopsy confirmed amyloidosis
  - Genetic testing showed positive TTR-S77T mutation

Patient #3

- 65yoM presented with several years history of bilateral feet and legs sensory symptoms, and had a prior diagnosis of bilateral CTS.
- Noted to have postural lightheadedness, and chronic diarrhea prior neuropathy diagnosis.
- He was diagnosed with symmetrical sensorimotor axonal neuropathy, based on his EMG/NCS.
- About 8 years after neuropathy diagnosis, his brother developed CHF, and reported his father had CHF at younger age.
- Cardiac work up suspected cardiac amyloid.
- TTR sequencing showed positive T80A mutation.

Patient #4

- 74yoM with 8 year history of constipation and bloating who presented with numbness in hands and feet, and was diagnosed with symmetrical sensorimotor axonal neuropathy.
- Several years after his diagnosis of peripheral neuropathy, he started having worsening SOB and was diagnosed with CHF.
- Cardiology suspected cardiac amyloid.
- TTR sequencing showed Val122Ile

Patient #5

- 65yo M, presented with 8-10 years history of hands and feet numbness and burning pain and mild balance impairment. Was suspected to have peripheral neuropathy and was diagnosed with small fiber neuropathy.
- Started developing dyspnea initially thought to be COPD but later found to be diastolic heart failure.
- He has history of elevated LFTS prompting liver biopsy showing amyloid deposition.
- Genetic testing showed TTR mutation Val42Ile.

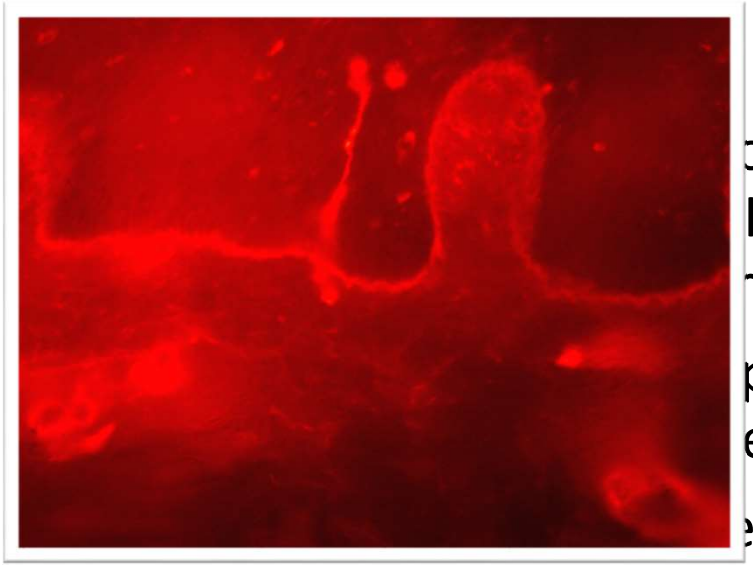
Patient #6

- 66yoM presented with several years history of hands and feet numbness and lower extremity weakness. Was diagnosed with peripheral sensorimotor axonal neuropathy.
- Developed orthostatic intolerance during the course of his neuropathy.
- Started having progressive dyspnea.
- Cardiologist performed echo showing **left ventricular hypertrophy**. Cardiac biopsy suggested TTR amyloidosis.
- TTR sequencing showed VaL122Ile mutation.

The University of Texas at Austin
Dell Medical School

Austin Neuromuscular Center

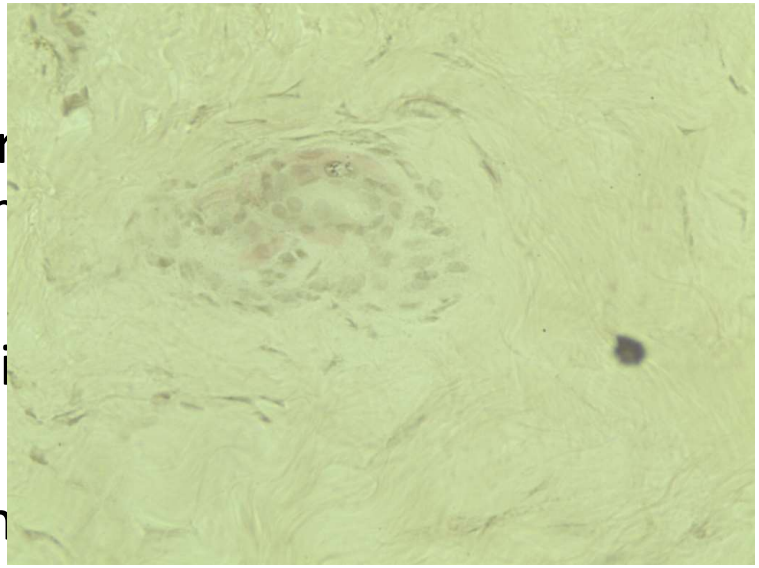
Patient #7



of bilateral car
His neuropath
ropathy.

pathy evaluati
erved EF.

ed IENFD, with



- Cardiac biopsy was suggestive of TTR amyloid.
- TTR sequencing showed TTR-Val122Ile

The University of Texas at Austin
Dell Medical School

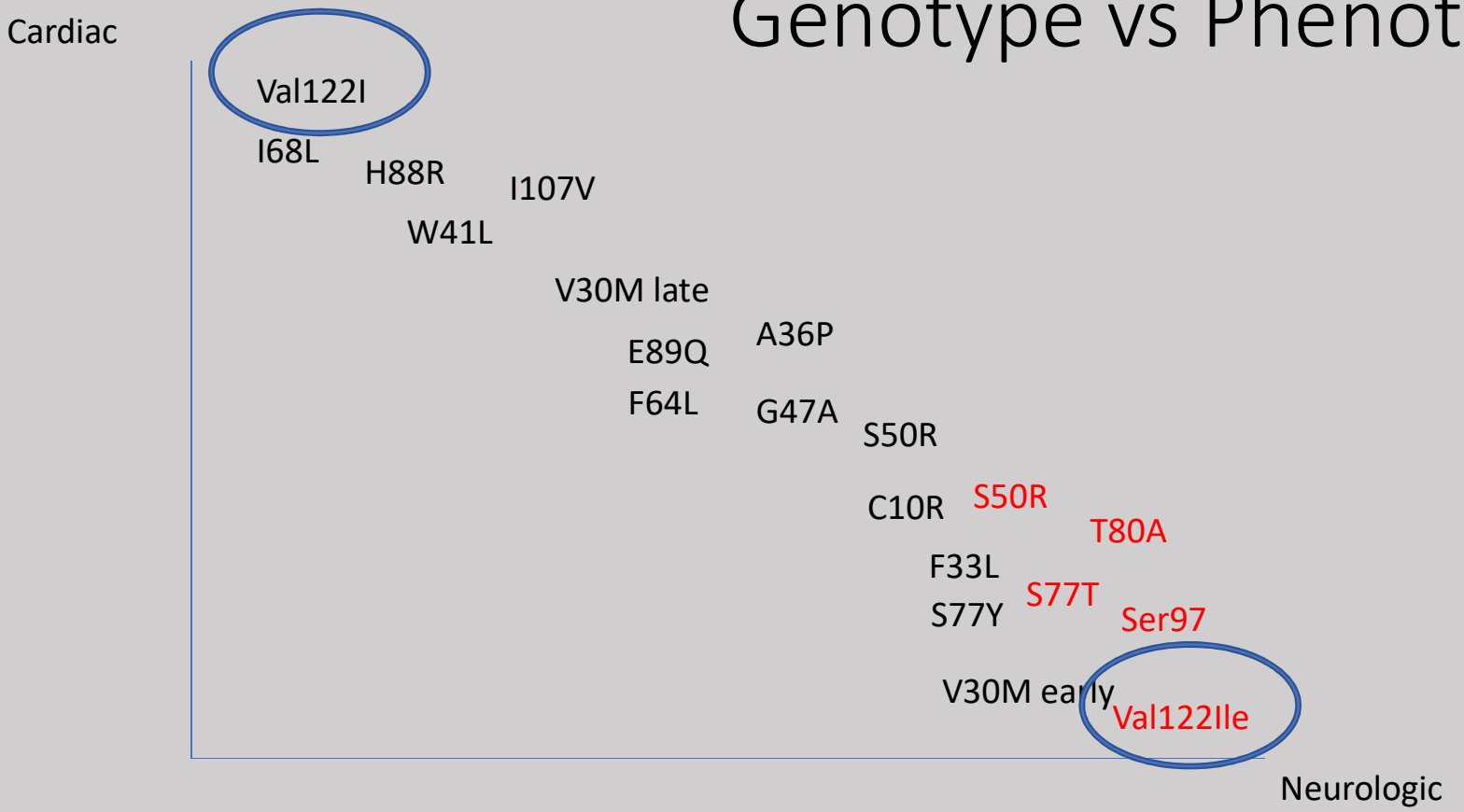
Austin Neuromuscular Center

Patient #8

- 47yoM with presented with 5 years history of lower extremities weakness and feet numbness/burning.
- Noted having significant Quads atrophy with difficulty climbing stairs and frequent falls due to knee “buckling”
- He was diagnosed initially with myopathy? No biopsy done.
- EMG showed proximal myopathic changes
- During the course of his evaluation, started developing severe ankle edema.
- Found to have CHF and later diagnosed with “infiltration cardiomyopathy”
- His brother started developed similar symptoms and diagnosed with CHF.
- Cardiology suspected a diagnosis of cardiac TTR amyloidosis
- Genetic testing confirmed HaTTR-S50R mutation

Patient	Initial presentation	Initial diagnosis	Red flag	Approximate Years to final diagnosis
1	Muscle weakness (Quads atrophy and grip weakness)	IBM	Diastolic heart failure	2
2	CIDP mimic	CIDP	Diastolic heart failure	3
3	Hands and feet sensory symptoms and postural intolerance.	Idiopathic sensorimotor axonal neuropathy.	Family history	8
4	Hands and feet sensory symptoms	Idiopathic sensorimotor axonal neuropathy.	CHF	8
5	Hands and feet sensory symptoms	Idiopathic small fiber neuropathy.	CHF	10
6	Hands and feet sensory symptoms	Idiopathic sensorimotor axonal neuropathy.	SOB and LVH	4
7	Hands and feet sensory symptoms	Idiopathic small fiber neuropathy	CHF	5
8	Muscle weakness (Quads atrophy and proximal weakness)	Myopathy	Family history and CHF	7

Genotype vs Phenotype



The University of Texas at Austin
Dell Medical School

Austin Neuromuscular Center

Several type of amyloidosis

- Primary (AL amyloidosis)
  - Plasma cell dyscrasia leading to overproduction of Immunoglobulin light chains (κ or λ)
  - Most common type
  - Peripheral and autonomic neuropathy (20%), Cardiac involvement up to 50%.
  - M Protein in serum and urine immunofixtion.
- Secondary (AA amyloidosis)
  - Deposition of fragments of serum amyloid A protein, an acute phase reactant
  - Associated with chronic inflammatory disorders (eg RA).
  - Almost never produces clinically apparent heart disease (< 5%)
  - No peripheral neurological involvement.
- Senile systemic amyloidosis (ATTRwt)
  - Transthyretin (normal) deposits.
  - Cardiac involvement and carpal tunnel syndrome.
  - 90% in men > 60 years of age.
- Hereditary amyloidosis:
  - Transthyretin related (second most common after AL amyloidosis)
  - ApoA1; FAP III (Iowa type)
  - Gelsolin; FAP IV (Finnish type)
- Other: Localized AL amyldosis – amyloid deposits at a single site – bladder, skin, larynx, lung

Hereditary TTR Amyloidosis

- Transthyretin (TTR) related
- 125 identified mutations
- Binds/transports thyroxine and retinol
- 1/3 have affected parent, 2/3 new point mutation
- Variable presentations

Hereditary TTR Amyloidosis

Neuropathy- sensory, motor, autonomic, small fiber neuropathy, carpal tunnel, slowly progressive

Cardiac- restrictive cardiomyopathy, USUALLY right sided heart failure but not always the case

Leptomeningeal- CNS symptoms (seizures, headache, myelopathy etc.)

Treatment:

Liver and/or cardiac transplant

TTR stabilizers- diflunisal, tafamidis

TTR gene silencers- patisiran, inotersen

Acquired Amyloidosis

- AL protein- Immunoglobulin light chains
- Associated with MGUS, multiple myeloma

Clinical syndromes:

Polyneuropathy

Autonomic failure

Mononeuritis multiplex

Myopathy

Systemic:

Cardiomyopathy

Nephrotic syndrome

Diarrhea

Anemia

Acquired Amyloidosis

Worse prognosis with cardiac and/or renal involvement

Mean survival 1-10 years

Gradual progression of symptoms

Treatment:

High dose chemotherapy

Peripheral blood stem cell transplant

Take Home Points

- HaTTR amyloidosis can mimic several common neuromuscular disorders at initial presentation.
- Presenting symptoms are diverse and involving multiple organ systems
- Delay in diagnosis will impact morbidity/mortality
- Remaining vigilant in diagnostic pursuit will save patients time, money, stress

References

- Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. Arch Neurol. 2005;62:1057-62
- Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants. Amyloid. 2003;7:54-69
- Jin K, Sato S. Familial leptomeningeal amyloidosis with a transthyretin variant Asp18Gly representing repeated subarachnoid hemorrhages with superficial side rosins. J Neurol Neurosurg Psychiatry. 2004;75:1463-6.
- Nakazato M. Genotype-phenotype relationship in familial amyloid polyneuropathy. Neurol Med (Tokyo). 1998;48:528-34.
- Ng B, Connors LH, Davidoff R. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. Arch Intern Med 2005;165: 1425-9.
- Sekijima Y. First nationwide survey on systemic wild-type ATTR amyloidosis in Japan. Amyloid. 2018;25:8-10
- Sekijima et al. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom cluster and treatment algorithm. Journal of rare diseases (2018)13:6.
- Vieira M, Saraiva MJ. Transthyretin: a multifaceted protein. Biomol Concepts 2014;5:45–54.
- Vita G. Recurrent syncope as persistently isolated feature of transthyretin amyloidotic polyneuropathy. Neuromuscul Disordering. 2005;15:259-61