A WOMAN WITH PAINLESS AND PROGRESSIVE WEAKNESS

VEDANARAYANAN, V. [1] **& SAN LUIS, C.** [2]

[1]DEPARTMENT OF NEUROLOGY, V.A. SONNY MONTGOMERY, JACKSON, MS; [2] DEPARTMENT OF NEUROLOGY, UNIIVERSITY OF MISSISSIPPI MEDICAL CENTER, JACKSON, MS

INTRODUCTION

- CMT are hereditary motor **and sensory** neuropathies classified into:
  - CMT1 – demyelinating
  - CMT2 – axonal
  - Dominant Intermediate CMT (DI-CMT) - axonal and demyelinating
- Dynamin-2 (DNM2)
  - Ubiquitous GTPase proteins that function in endocytosis, transport of vesicles, vesicle budding, organelle fission and fusion
  - Acts with other proteins such as ampiphysin and actin-binding proteins
- DNM2 mutation leads to:
  - **CMT2M and DI-CMT**
  - Centronuclear myopathy
  - Hereditary spastic paraplegia
- CMT2 and DI-CMT present with:
  - Distal progressive weaknes
  - **Sensory deficits**
  - Decreased or absent tendon reflexes

We present a case of progressive weakness **with minimal or no sensory symptoms** with **diagnostic studies consistent with a motor neuron disease** and neurogenic myopathy

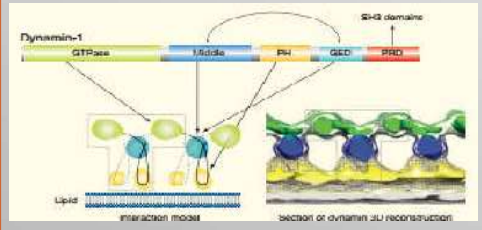

FIGURE 1. Model PRD-less dynamin-1
Heymann, J. A., & Hinshaw, J. E. (2009). Dynamins at a glance. Journal of cell science, 122(Pt 19), 3427-31.

CASE DESCRIPTION

History:

- 24 yo female who presented with progressive worsening weakness for the past 7 years.

Chair → stairs → now wheelchair bound

- Had dyspnea, occasional dysphagia, urinary retention, and constipation.
- **Denied sensory loss**
- No muscle cramps or spasms
- Born full term and achieved her motor milestones appropriately
- She had some mild cognitive delay
- Attended high school with special assistance online programs
- Denies family history of similar condition

Examination:

- Wheel chair bound, follows commands, nasal speech and mild dysarthria.
- Mild ptosis of both eyes
- Bilateral equinovarus with mild muscle atrophy in her hands
- **Pinprick, temperature, vibration, position intact**

TABLE 1. Medical research council grade (MRC) of motor strength

BILATERAL		BILATERAL	
Deltoids	5/5	Hip Flexion	2/5
Biceps	4-/5	Knee Extension	4-/5
Triceps	3/3	Knee Flexion	4/5
Finger flexion	5/5	Dorsiflexion	3/5
Finger extension	3-/5	Plantar Flexion	2/5
Finger abduction	3/5	Toe extension	3-/5
		Toe Flexion	4+/5

RESULTS

Table 2. Sensory and Motor Nerve Conduction Studies

EMG NCS with diffuse active and chronic denervation in multiple muscles consistent with motor neuron disease . No electro-diagnostic evidence of myopathy and large fiber polyneuropathy.

Type of study	Side/ Nerve	Stimulation Site	Recording site	Latency (ms)	AMP (mV)	Duration (ms)	Distance (mm)	Conduction velocity (m/s)
Motor	R Median	Wrist	APB*	3.2	5.6	5.9	70	
		Elbow	Wrist	6.9	4.1	6.7	210	57
Motor	R Ulnar	Wrist	ADM*	2.4	6.7	6.5	70	
		Below Elbow	Wrist	5.8	6.5	6.9	200	59
		Above Elbow	Below Elbow	7.3	5.3	7.2	110	73
Motor	R Peroneal	Ankle	EDB*	3.3	0.8	6.2	80	
		Fibula	Ankle	11.1	0.4	8.4	310	40
Motor	R Tibial	Ankle	Abductor Hallucis	4.0	6.5	3.9	80	
		Popliteal fossa	Ankle	12.7	2.3	4.9	390	45
Sensory	R Median	Wrist	Digit II	2.7	107	0.7	130	64
Sensory	R Ulnar	Wrist	Digit V	2.5	77	0.8	110	66
Sensory	R Radial	Forearm	Snuff box	1.9	40	0.7	100	83
Sensory	R Sural	Lower leg	Ankle	2.5	11	0.6	130	68

**APB - abductor pollicis brevis, ADM – Abductor digiti minimi, EDB – extensor digitorum brevis*

Negative Laboratory Results:
Blood count, electrolytes, Folate, Vitamin B12, TSH, liver function tests and CK were normal and **Survival motor neuron gene 1 (SMN1)** mutation

Pending pathology

Figure 2. Muscle biopsy
With variable fiber size and occasional atrophic and angulated fibers. No group atrophy or perifascicular atrophy. Internalized nuclei were not increased. No inflammatory infiltrates. Consistent with neurogenic myopathy without inflammation.

Next generation sequencing:
(+) Dynamin 2 mutation

DISCUSSION OF RESULTS

- CMT2M and DI-CMT both present with:
  - Distal weakness and atrophy
  - Decreased or absent tendon reflexes
  - **Decreased temperature, vibration and/or position sense**
- CMT2M has normal NCV while CMTDIB has both reduced nerve conduction and action potentials
- We present **this novel case who had minimal or no sensory symptoms**

- Distal hereditary motor neuropathies (dHMN) are pure motor hereditary neuropathies with normal sensory potentials and without sensory complaints
- dHMN so far has not been associated with DNM2 mutations
- One study looked at 105 patients and found overlapping genes in CMT2 and dHMN
  - **Dynamin 2 mutation however was found only in CMT2**

The question:
Is DNM2 just found exclusively in CMT2M or also in dHMN? Or is dHMN really just another CMT?

CONCLUSION

This novel case of dynamin 2 mutation presenting as chronic progressive weakness with minimal or no sensory loss may be another example of the existence of gray areas in CMT and dHMN classification. Documentation of these may enlighten us further in classification of these diseases.

REFERENCES

Tanabe K, Takei K. Dynamin 2 in Charcot-Marie-Tooth disease. Acta Med Okayama. 2012;66(3):183-90. Review. PubMed PMID: 22729098.

Renwick NM, Goldfarb LG, Sambuughin N, Hinshaw JE, Toro C, et al. (2016) Progressive Neuromuscular Syndromes Linked to Dynamin-2 Mutations. J Mult Scler (Foster City) 3:163. doi:10.4172/2376-0389.1000163

Garg N, Park SB, Vucic S, et al Differentiating lower motor neuron syndromes J Neurol Neurosurg Psychiatry 2017;88:474-483.

Bansagi, B., Griffin, H., Whittaker, R., Antoniadi, T., Evangelista, T., et.al. (2017). Genetic heterogeneity of motor neuropathies. Neurology, 88(13), 1226-1234. doi:10.1212/WNL.0000000000003772