A Patient with Long-Standing Weakness

41st Carrell-Krusen Symposium

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- 28 y/o female with long-standing weakness and nasal speech.
- Patient first noticed weakness as young as pre-K years when she had difficulty walking up the steps of the school shuttle. Currently, she has trouble climbing up the stairs and also getting out of chair/toilet seat. She is able to comb her hair without getting tired.
- Regarding nasal speech, she has had it as long as she could remember. She was told to that she had a submucosal cleft palate and had done surgery at the age of 25.

- **Past Medical History:**
- Long-standing weakness , cleft palate

- **Past Surgical History:**
- Tonsillectomy
- Surgery for cleft palate

- **Family History:**
- Has 5 brothers. She is the youngest.
- One brother cannot run as fast as other brothers. His weakness is mild
- No consanguinity in parents

- **Social History:**
- Lives with parents. Denies illicit drugs , alcohol and tobacco abuse

Birth and early childhood history

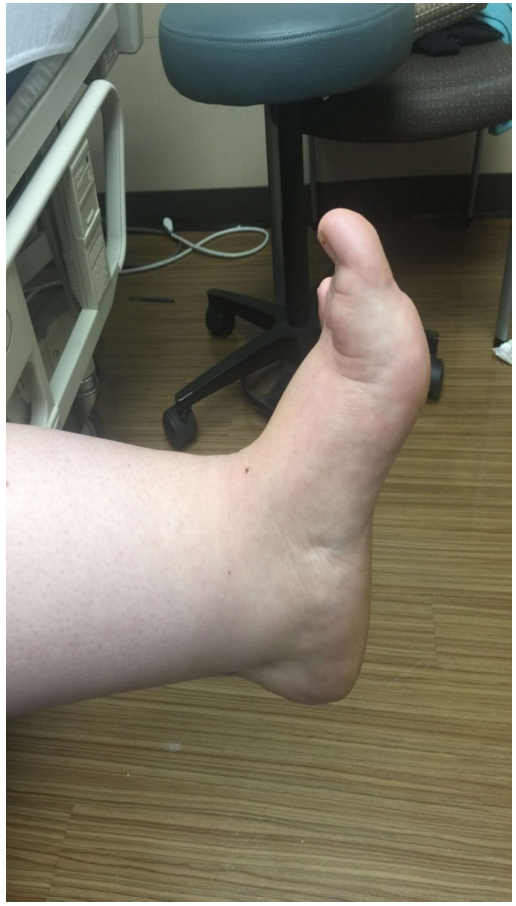
- Born term via C-section. Had to stay in hospital for jaundice and a feeding problem for a week.
- Her mom never felt her move when she was pregnant with patient. No problem was observed during U/S visits.
- Patient never required a feeding tube but had to be fed very slowly with small amounts during the neonate period.

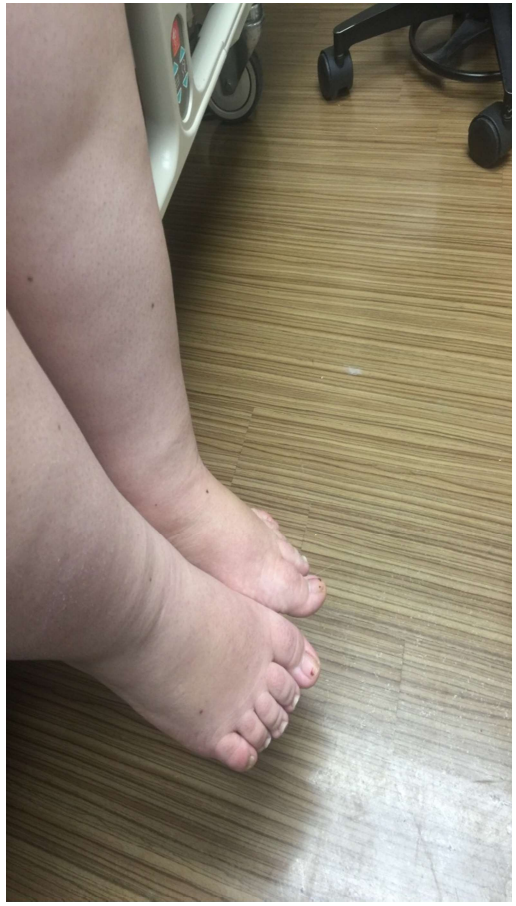
Review Of Systems

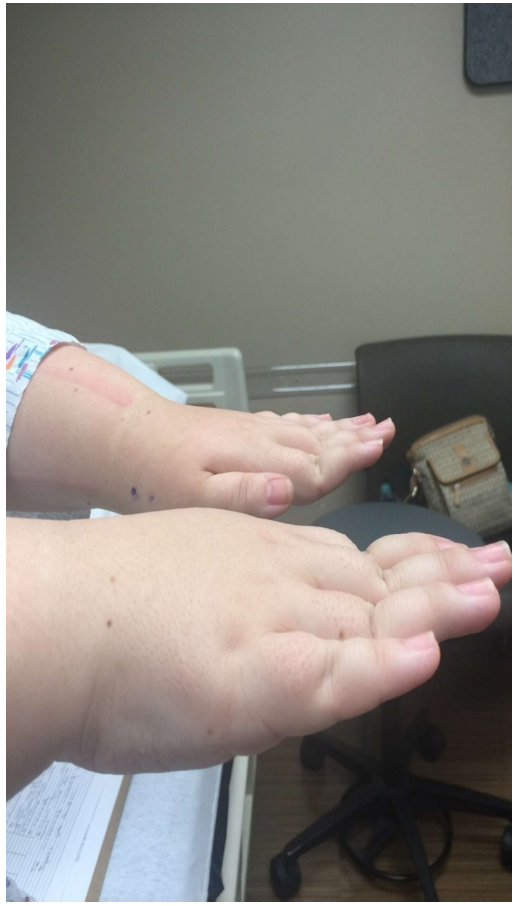
- Denies shortness of breath, double vision, dysphagia , paresthesia , hearing problems, sphincter incontinence.
- Positive for heart murmur and palpitation (no abnormality in 30-day holter monitoring and normal echo).
- Has dermatographism

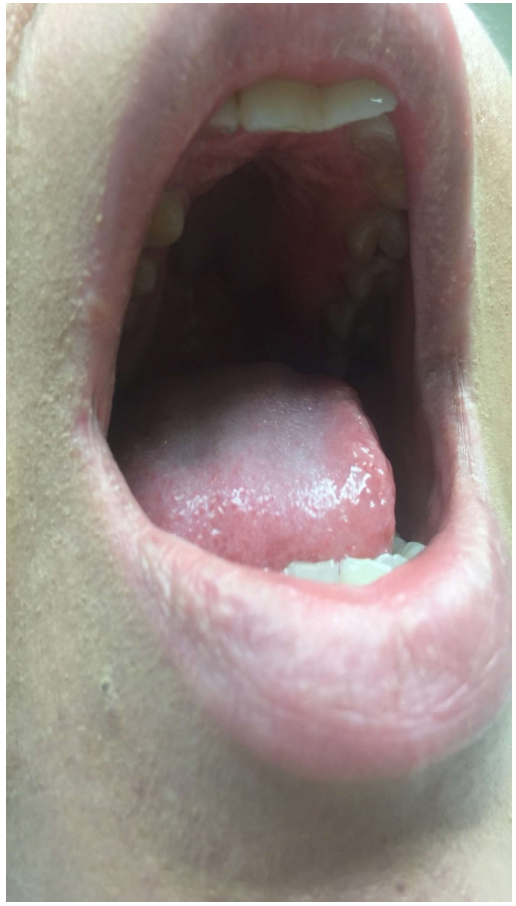
Physical Exam

- **General :**
- Normal appearance , normal funduscopic exam, normal lung and heart auscultation , soft abdomen with present bowel sounds
- **Neurology :**
- Mental status : normal (AAO X3)
- Cranial Nerves :nasal speech and high arched palate , otherwise normal
- Motor : B/l biceps , deltoid and iliopsoas weakness with mild neck flexor weakness (4/5) . Distal hand weakness (finger extensor and interossei) 4/5.
- Reflexes : 2+ and symmetric muscle stretch reflexes.
- Plantar response:Flexor b/l.
- Sensory and Cerebellar: Normal
- Gait : Normal









Assessment

- This is a 28 y/o patient with long standing weakness who on exam has nasal speech, high arched palate, proximal and distal weakness in upper extremities and proximal weakness in lower extremities. Family history suggests a brother who might have the similar disorder.

DDx? Next Step?

EMG Summary

EMG Summary Table											
	Spontaneous					MUAP				Recruitment	
Muscle	IA	Fib	PSW	Fasc	Other	Poly	Amp	Dur.	Rate	Pattern	Effort
L. Abductor digiti minimi (manus)	Normal	0	0	0	None	None	Normal	Normal	Normal	Normal	Normal
L. Tibialis anterior	Normal	0	0	0	None	Mod	Normal	Normal	Normal	Normal	Normal
R. Vastus lateralis	Normal	0	0	0	None	Few	Normal	Normal	Normal	Normal	Normal
L. Iliopsoas	Normal	0	0	0	None	Few	Normal	Normal	Normal	Early	Normal
R. Biceps brachii	Normal	0	0	0	None	Few	Normal	Normal	Normal	Mild Early	Normal
L. First dorsal interosseous	Normal	0	0	0	None	None	Normal	Normal	Normal	Normal	Normal
L. Deltoid	Normal	0	0	0	None	Few	Normal	Normal	Normal	Mild Early	Normal

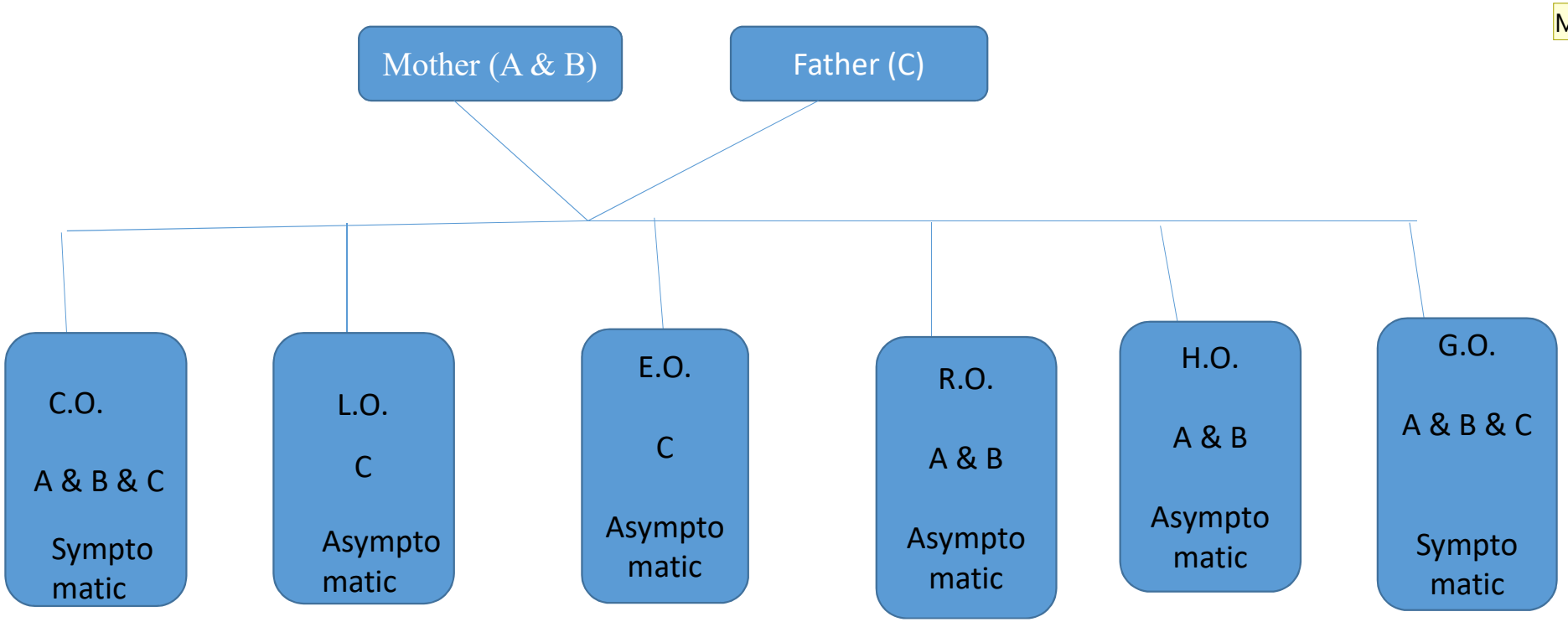
Genetic Testing

- Sequence analysis and detection/duplication testing of the 28 genes listed below for congenital myopathy :
- ACTA1,BIN1,CCDC78,CFL2,CNTN1,COL12A1,COL6A1,COL6A2,COL6A3, DNM2,FKBP14,KBTBD13,KLHL40,KLHL41,LMOD3,MEGF10,MTM1,MYF 6,MYH7,MYPN,NEB,RYR1,SELENON,STAC3,TNNT1,TPM2,TPM3,TTN.
- Results are negative except for NEB gene:
- One pathogenic variant and two variants of uncertain significance identified in NEB.

Genetic Testing

		Variant	Zygosity	Variant Classification
Mother	**A**	c.13756C>T (p.Gln4586*)	unknown	PATHOGENIC
Mother	**B**	c.22075A>C (p.Lys7359Gln)	heterozygous	Uncertain Significance
Father	**C**	c.8020G>A (p.Glu2674Lys)	heterozygous	Uncertain Significance

Genetic Testing



Slide 15

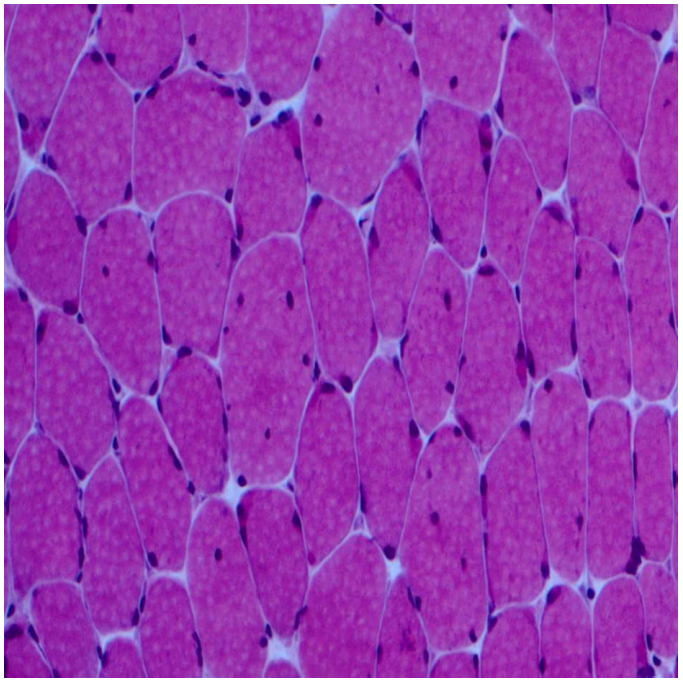
MS1 Mahan Shahrivari, 02/18/2019

Genetic Testing

- **c.13756C>T is pathogenic variant.**
- This sequence change creates a premature translational stop signal (p.Gln4586*) in the NEB gene. It is expected to result in an absent or disrupted protein production.
- c.22075A>C and c.8020G>A are two variants of unknown significance.

Genetic Testing

- Both parents and other siblings (5 brothers) then were tested.
- The only brother with milder symptoms has same genetic test result as our patient with one pathogenic variant and two variant of unknown significance.
- Asymptomatic brothers have inherited variants (one or two) from either parents but not from both.
- It was found that pathogenic variant (c.13756C>T) and variant c.22075A>C were inherited from mother and variant c.8020G>A was inherited from father.



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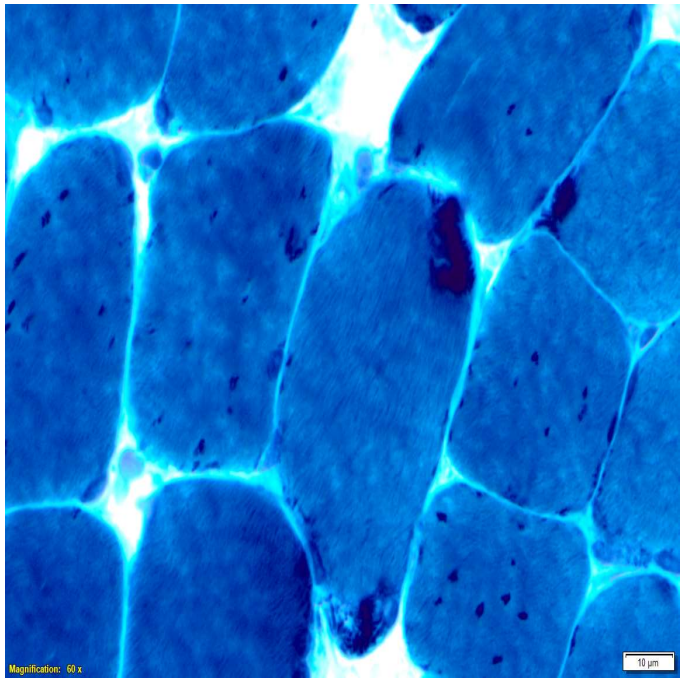
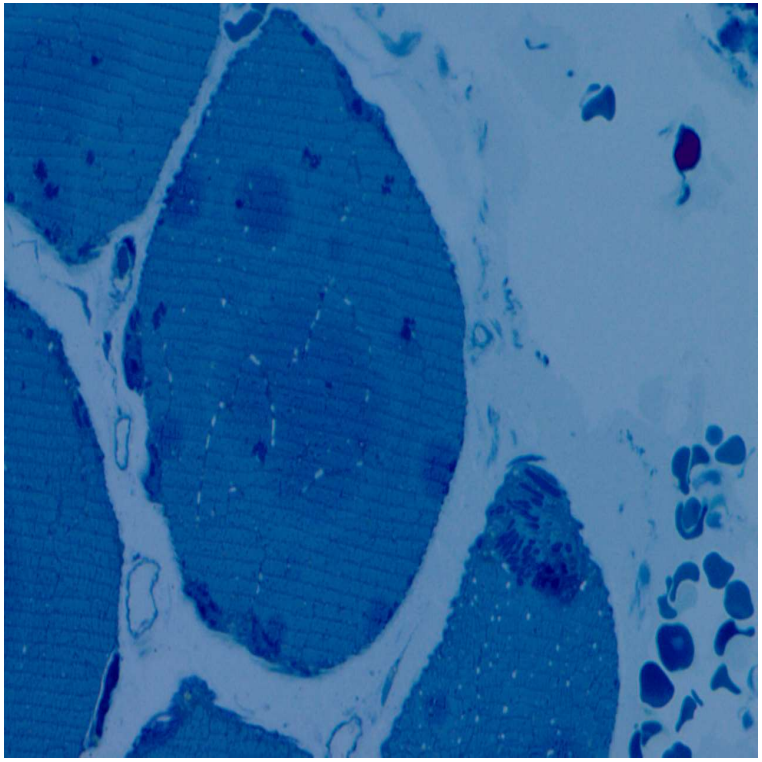


Modified Trichrome



Semithin

Nemaline Myopathies

- First described in an infant girl with early-onset hypotonia and muscle weakness.
- Nemaline myopathy has an incidence of 1:50,000 live births, although it may be more common in certain populations (e.g. in Ashkenazi Jews, or in the Amish community)
- Nemaline myopathy is called due to threadlike (nema refers to thread) or rodlike structures in muscle biopsy.
- Clinic spectrum is wide, ranging from a severe congenital form to mild adult-onset nemaline myopathy.
- Prominent axial and limb-girdle weakness occurs initially , followed by progression to distal muscles.

Nemaline Myopathies

- Neonatal-onset or classic form which is more severe form accounts for 16% of all cases. These patients are hyposthenic, hypotonic from birth and have difficulty sucking and swallowing. Respiratory failure or aspiration pneumonia will often lead to death in the first months of life.
- However most common form is less severe being characterized by weakness of the limbs, trunk and facial muscles and by slowly progressive disease course. Motor milestone is delayed. Muscle hypotonia is always present during the first year of life. These patient have distinctive facial features due to head muscles weakness including elongated face, high-arched palate and tented upper lip. Most patients have predominant proximal weakness; however distal-predominant involvement also has been seen in late-onset cases
- Respiratory involvement is the main prognostic factor.

Nemaline Myopathies

- Currently, 10 genes have been associated with nemaline myopathy including:
- ACTA1 (dominant mutations of skeletal muscle alpha-actin 1)
- NEB (recessive mutations of nebulin genes)
- CFL2 (muscle-specific cofilin 2)
- TNNT1 (troponin T1 slow skeletal type)
- TPM2 (Beta-tropomysin 2)
- TPM3 (alpha-tropomyosin 3)
- KLHL40 (kelch-like family member 40)
- KLHL41 (kelch-like family member 41)
- KBTBD13 (muscle-specific ubiquitin ligase genes)
- LMOD3 (recessive mutations of leiomodin)

Nemaline Myopathies

- Mutations in the *NEB* gene encoding nebulin, inherited in an autosomal recessive manner, are the most frequent (accounting for over 50%), followed by mutations in *ACTA1*(around 20%) encoding alpha-actin 1.

Take-Home Message

- Since many genetic testing panels are free of charge to patients, and are now available to us as clinicians, genetic testing has become the first line laboratory investigation in many cases. Yet this does not exclude the need for clinical reasoning and interpreting all data including pathology.


Thank
you