5-YEAR-OLD BOY WITH PROGRESSIVE PROXIMAL WEAKNESS AND HYPOTONIA

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CASE PRESENTATION

5 year-old Hispanic boy presented with:

- 4 months of progressive leg pain, falls, head and leg weakness
- Requiring support to walk up stairs
- Would push on his legs to rise from the floor
- Requiring help to raise his head from chest
- No issues with bowel, bladder, breathing, or appetite

Pertinent history:

- Limited febrile mononucleosis 5 months prior
- Normal birth history and milestones
- Family history remarkable for 3 healthy siblings and 1 maternal cousin who died at age 6 years who could not move well and required total care

EXAM FINDINGS

General: Short stature (1-2nd%ile)

Cranial nerves: Normal

Bulk: Muscle wasting over torso/upper scapula

Tone: Head and trunk hypotonia

Strength: **Proximal pattern upper and lower extremity weakness**

- weak shoulder shrug
- neck flexion/extension 3/5
- deltoids 3/5
- biceps/triceps 4+/5
- hand grip 5/5
- hip flexors 4-/5
- quads/ hamstrings 4/5
- dorsiflexion 4-/5
- plantar flexion 4/5

DTR: 1+ Reflexes throughout

Gait: Lordotic, waddling, + Gower's sign

DIFFERENTIAL DIAGNOSIS

- Neuronopathies: SMA, juvenile ALS
- Neuropathies: AIDP, CIDP,
- NMJ: Myasthenia (Genetic, immune)
- Myopathies: Dystrophic, congenital, mitochondrial, metabolic (Pompe)

NCS/EMG STUDY

Sensory Nerve / Sites	Rec. Site	Onset Lat	Peak Lat	NP Amp	Segments	Distance	Vel. Pk	Vel.
R Median - Digit II (Antidromic)		ms	ms	µV		cm	m/s	m/s
Wrist	Dig II	1.56	2.14	87.0	Wrist - Dig II	11	51.5	70.4
R Ulnar - Digit V (Antidromic)								
Wrist	Dig V	1.30	2.19	37.0	Wrist - Dig V	9	41.1	69.1
R Sural - Ankle (Calf)								
Calf	Ankle	1.98	2.50	33.9	Calf - Ankle	12	48.0	60.6
L Sural - Ankle (Calf)								
Calf	Ankle	2.08	2.60	30.1	Calf - Ankle	12	46.1	57.6

Motor Nerve / Sites	Muscle	Latency	Amplitude	Segments	Distance	Lat Diff	Velocity	Temp.
R Median - APB		ms	mV		cm	ms	m/s	°C
Wrist	APB	2.45	7.0	Wrist - APB	7			34.5
Elbow	APB	4.38	7.6	Elbow - Wrist	10	1.93	52	34.8
Upper arm	APB	5.63	6.5	Upper arm - Elbow	7.5	1.25	60	
R Peroneal - EDB								
Ankle	EDB	2.55	6.2	Ankle - EDB	6			
Fib head	EDB	5.21	6.0	Fib head - Ankle	16	2.66	60	
Pop fossa	EDB	6.04	5.3	Pop fossa - Fib head	6	0.83	72	

Anatomy / Train	Rate	Ampl.	Ampl 4-1	Fac Ampl	Area	Area 4-1	Fac Area	Time
R Ulnar - ADM	Hz	mV	%	%	mVms	%	%	
Baseline	3	6.0	-0.7	100	15.6	2.5	100	0:00:00
1 min after Baseline	3	6.0	-1	99.6	15.4	1.4	98.7	0:01:07
Exercise	50	6.1	-26	101	15.7	-145	101	0:02:38
Immediate after Exercise	3	6.1	-0.4	101	15.7	1.5	101	0:02:54
30 secs post exercise	3	6.1	-0.3	101	15.8	1.8	101	0:03:15
4 min post exercise	3	6.0	-0.1	99.5	15.7	2.7	100	0:06:49
R Accessory (spinal) - Trapezius								
Baseline	3	3.1	1.2	100	21.5	1.2	100	0:00:00
1 min after baseline	3	3.1	0.9	99.7	21.5	2.9	100	0:01:04

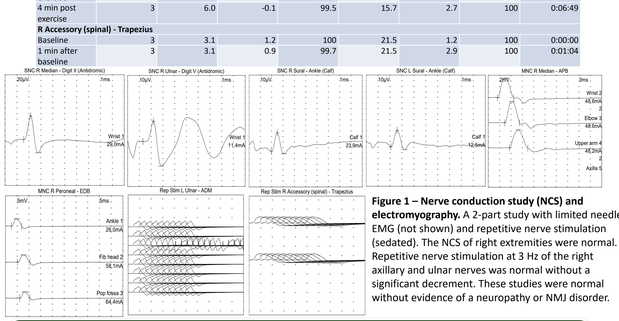

Figure 1 – Nerve conduction study (NCS) and electromyography. A 2-part study with limited needle EMG (not shown) and repetitive nerve stimulation (sedated). The NCS of right extremities were normal. Repetitive nerve stimulation at 3 Hz of the right axillary and ulnar nerves was normal without a significant decrement. These studies were normal without evidence of a neuropathy or NMJ disorder.

MUSCLE BIOPSY FINDINGS

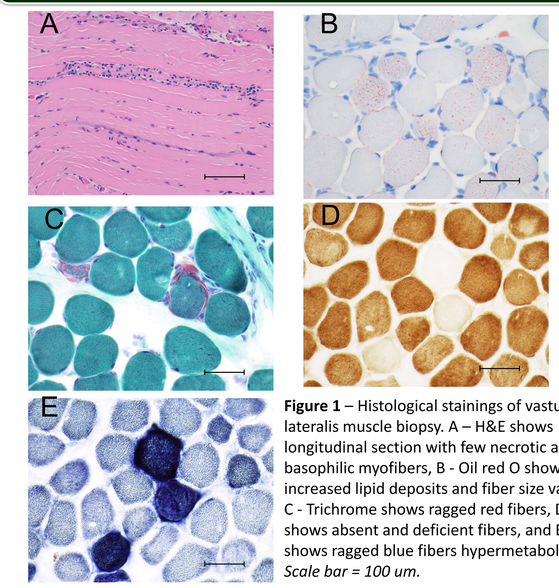

Figure 1 – Histological stainings of vastus lateralis muscle biopsy. A – H&E shows longitudinal section with few necrotic and basophilic myofibers, B - Oil red O shows increased lipid deposits and fiber size variation, C - Trichrome shows ragged red fibers, D - COX shows absent and deficient fibers, and E - SDH shows ragged blue fibers hypermetabolic fibers. *Scale bar = 100 um.*

IMAGING, LAB, & MOLECULAR RESULTS

- Labs: Creatine Kinase **= 511 U/L** (30-200), C-reactive protein= 0.79 (0-0.50), Lactic Acid 2.1 (0.5-2.2), CSF studies/cultures normal and CSF protein 15.3 (15-40).
- Echocardiogram/EKG, MRI brain/spine unremarkable.
- Genetics (Blood): Invitae Comprehensive Neuromuscular Disorders panel: VUS within *RYR*. gene. Juvenile ALS panel: negative.
- Genetics (Muscle): Mitochondrial Respiratory Chain Enzyme: negative. BCM-MitoNGS Comprehensive mtDNA: multiple low-level deletions. BCM-MitomeNGS Panel: **Homozygous pathogenic variant c.173A>G (p.N58S) in *TK2* gene.**

CLINICAL SUMMARY

Presentation: Progressive proximal weakness, diminished reflexes, +Gowers; elevated CK, CRP, normal lactic acid

Muscle Biopsy: Ragged red fibers (Fig 1C), intracellular accumulation of lipids (Fig 1B), stained hypermetabolic fibers (Fig 1E)

Genetics: Multiple low-level mitochondrial deletions suggestive of a primary mitochondrial myopathy

Mitochondrial genetics: Homozygous pathogenic variant c.173A>G indicating TK2 mitochondrial Depletion Syndrome

Management:

- Coenzyme Q10 at 10 mg/kg/day
- Gastrostomy tube for weight loss and poor oral intake
- MDA Care: Pulmonary and Rehabilitation services
- Cardiac and audiology evaluation
- Family genetic evaluation and counseling
- **Presently receiving compassionate-use nucleotide precursors deoxythymidine (dThd) and deoxycytidine (dCyt) therapy.**

DISCUSSION

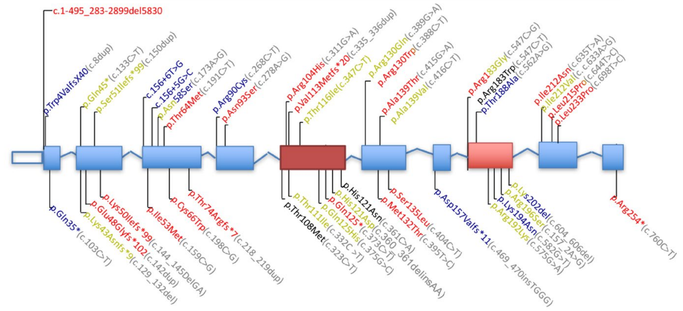

Figure 3 - Thymine kinase 2 (TK2) mutations. Mutations in the coding and splice-site regions of TK2 (NM_004614.4). Hot-spot exons are marked in red boxes. Protein changes are color-coded based on the clinical phenotype. Protein changes found with more than one clinical phenotype are highlighted with multiple colors. Protein changes found in all of the three forms are noted in black. DNA sequence variants are noted in grey font. Figure from Garone C, et al. J Med Genet 2018.

The *TK2* gene encodes thymidine kinase which is involved in production of mitochondrial DNA via recycling of nucleotides. Deficiency leads to an imbalance in pool of DNTs. There are 3 recognized phenotypes with variable onset, severity, and survival: The infantile-onset (<1 year) myopathy: rapid progression with high mortality. **Childhood onset (1-12 yo): moderate progression of proximal weakness, positive Gower's sign with high percentage (>50%) of wheelchair and/or ventilatory dependency.** Later onset (>12 yo): mild/slow progression

- Our case represents a diagnosis of childhood-onset mitochondrial myopathy / mitochondrial depletion syndrome due to TK2 deficiency
- Consideration of a diagnosis of mitochondrial myopathy in the setting of hypotonia, proximal progressive weakness, and short stature is warranted
- Early evaluation for TK2 deficiency by molecular testing can further direct the treatment options

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