Patient Case Study #3

Respiratory Presentation

HPI

63-year-old male presents to the neuromuscular clinic for evaluation of phrenic nerve paralysis and muscle weakness.

12 years ago he developed sub-acute respiratory insufficiency and required hospitalization. Difficulty going up stairs and getting up from a chair. Noted to have minimal movement of the right hemidiaphragm and reduced on the left. Testing suggested bilateral phrenic nerve palsies and underwent bilateral phrenic nerve stimulators. Complains of muscle pain and weakness of arms and legs, only able to walk a few steps. Has severe orthopnea and needing respiratory assistance while in the supine position.

SocHx

Not available

FamHx

Not available

PMHx

- Phrenic nerve paralysis with elevated right hemidiaphragm
- Nocturnal BiPAP
- Positive ANA & DS DNA antibodies
- Bilateral phrenic stimulators

Medications

Not available

Allergies

Not available

Exam

- Gen: NAD, VSS, unremarkable with no skin changes, organomegaly, or joint abnormalities
- MS: Alert & Oriented x 3, speech is clear and fluent, normal affect
- CN: PPERRLA, EOMI. Facial muscle strength and sensation are normal. Masseter and temporalis muscles are normal without atrophy. Palate is midline with normal tongue bulk and strength, and without fasciculations
- Motor: UE deltoid 4/5, biceps and triceps 4+/5, 5/5 distally bilaterally

  LE hip flexor 3/5 bilaterally, hamstring 4+/5 bilaterally, knee extensors 4+/5, ankle dorsiflexors/plantar flexors 5/5

  Atrophy of the quadriceps muscles bilaterally

  No fasciculations or hypertrophy were seen

  Normal muscle tone without hypertrophy
- Sensory: Intact to all modalities in the UEs and LEs
- Reflexes: Biceps, triceps, brachioradialis, quadriceps, and ankle reflexes are 1+. Babinski and Hoffmann signs are absent
- Coordination/Gait: No dysmetria in the UEs. No truncal ataxia. LE dysmetria testing was difficult to assess due to weakness. Gait is waddling and lordotic

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Labs/Diagnostics

CBC, CMP, ESR, ANA profile, RF, ANCA panel, TSH, B12, and CPK were all normal except for:

- Lactate 24.9 mg/dL [normal 4.5-19.8]
- Pyruvate 0.9 mg/dL [normal 0.3-0.7]
- CRP 24.1 mg/L [normal 0.0-4.9]
- GAA (DBS) 2.95 pmol/punch/h [normal >3.88]

Imaging

CT myelogram, negative for spinal cord compression.

EMG/NCV

Reported as normal.

PFT

Upright FVC was 41% predicted for age and gender, supine FVC was not performed due to severe orthopnea.

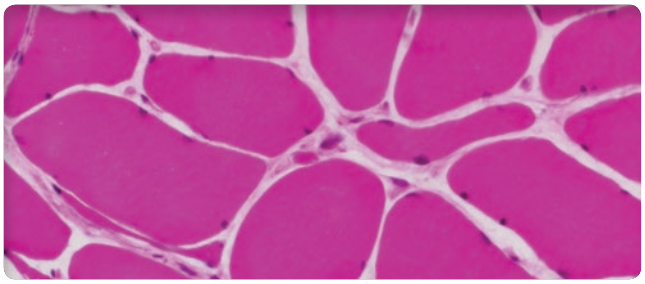
Genetic Analysis

Sequencing of the GAA gene revealed compound heterozygosity with the common intronic leaky splice site mutation c.-32-13T>G in intron 1 and a deletion c.2481+102-2646+31 in exon 18.

Pathologic studies

Left deltoid muscle biopsy showed non-specific myopathic changes without vacuoles or inflammation (figure 1).

Figure 1: Left deltoid muscle biopsy



Discussion

Respiratory pearls of LOPD

- Weakness of certain muscles including the diaphragm are suggestive of LOPD with a majority developing dyspnea and/or orthopnea of varying severity
- Respiratory involvement may precede limb-muscle involvement, occurring in approximately 10% of patients with late-onset Pompe[1]
- A respiratory presentation is likely not to be referred to a neurologist or neuromuscular specialist, leading to a delay in diagnosis
- Despite the recognition of diaphragm weakness as having a neuromuscular origin, a nerve disorder is more likely to be diagnosed, because respiratory neuromuscular testing is limited and has a difficult time distinguishing nerve from muscle disorders
- The respiratory complications of Pompe requires a more in-depth plan consisting of a combination of noninvasive ventilation, evaluation for nocturnal hypoventilation, and augmented cough devices[2]

Muscle biopsy and EMG testing

- A nondiagnostic muscle biopsy or EMG does not sufficiently exclude the diagnosis of LOPD
- A DBS GAA enzyme test should be performed regardless of the muscle biopsy or EMG results, to avoid delay in diagnosis and disease management

Critical aspects of late-onset Pompe disease

- The clinical features of a limb-girdle pattern of weakness, particularly affecting the thigh adductor and hamstring muscles, with paraspinal weakness and diaphragmatic dysfunction, should trigger the clinician to include GAA enzyme assay by DBS testing as part of the workup, regardless of EMG or muscle biopsy results

References: 1. Montagnese F, Barca E, Musumeci O, et al. Clinical and molecular aspects of 30 patients with late-onset Pompe disease (LOPD): unusual features and response to treatment. *J Neurol.* 2015;262(4):968-978. **2.** Ambrosino N, Confalonieri M, Crescimanno G, Vianello A, Vitacca M. The role of respiratory management of Pompe disease. *Respir Med.* 2013;107(8):1124-1132. **3.** Wokke JH, Escolar DM, Pestronk A, et al. Clinical features of late-onset Pompe disease: a prospective cohort study. *Muscle Nerve.* 2008;38(4):1236-1245. **4.** van der Ploeg AT, Barohn R, Carlson L, et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. *Mol Genet Metab.* 2012;107(3):456-461.

GZUS.PD.15.07.1924

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