4 Year Old Boy With Progressive Bulbar Weakness

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Initial ED Visit

- Mother reports patient with drooping eyelids since birth, originally attributed to chubby face
- Mother noticed he had a weak cry
- Had progressive propensity to fall
- Walked with foot drop
- Could eat but had difficulty swallowing since birth
- Had shortness of breath when climbing stairs
- Had difficulty moving his eyes
- Parents report he is not as smart as his older brother when he was at his age

Past Medical History

- Pregnancy History:
  - No known problems with pregnancy
  - Four day NICU stay for desaturations; did not require intubation and these problems resolved
- Diagnosed with tracheomalacia and asthma
- No medications

Developmental History

- Sat independently on time ~7 months
- Stood with support at 11 months
- Walked at 2 years, though with frequent falls
- Did not speak until 2 or 3 years
- Even at 4 years of age, he does not speak in full sentences
- Slower with learning than his older siblings at the same age

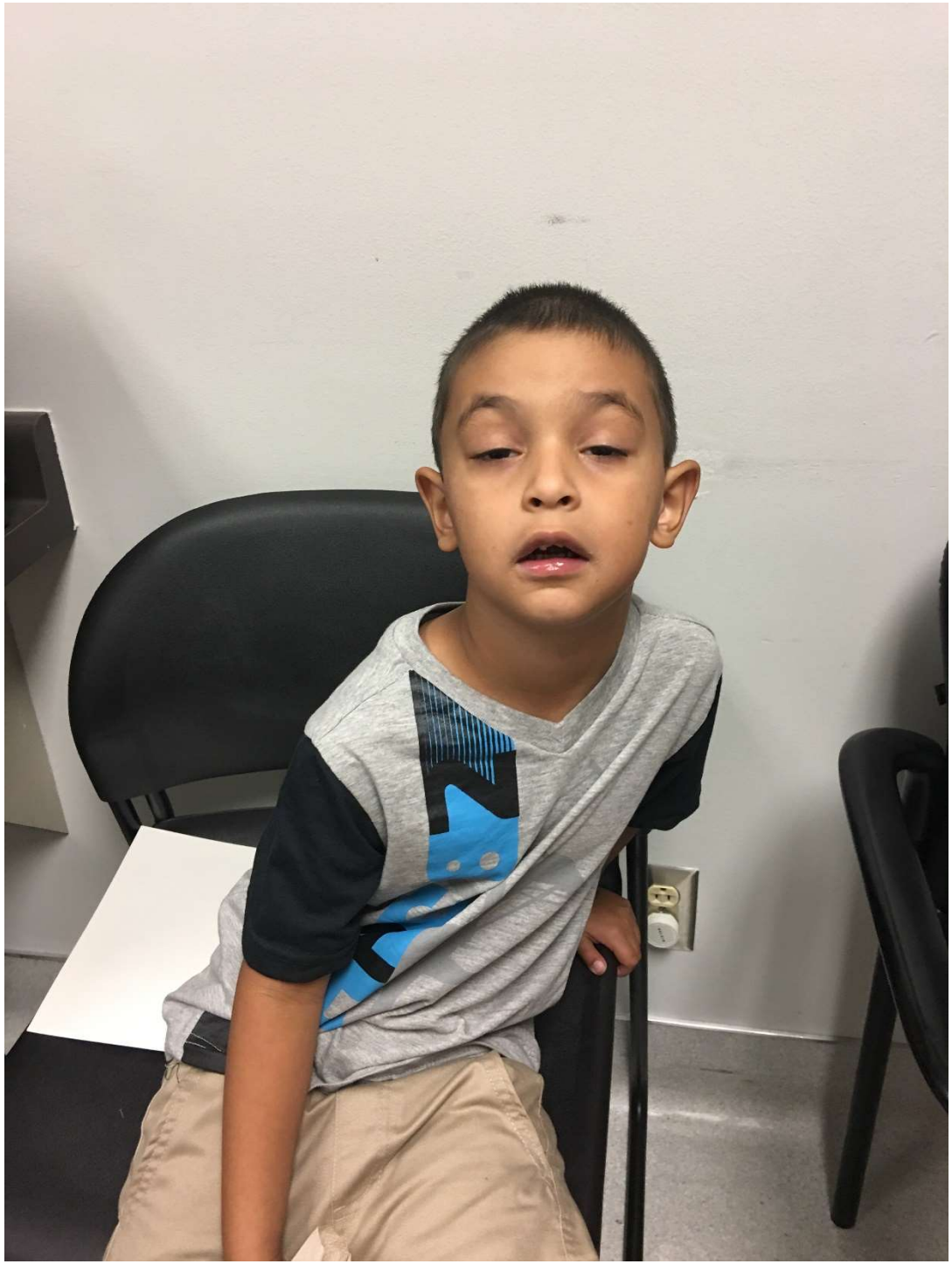
Other History:

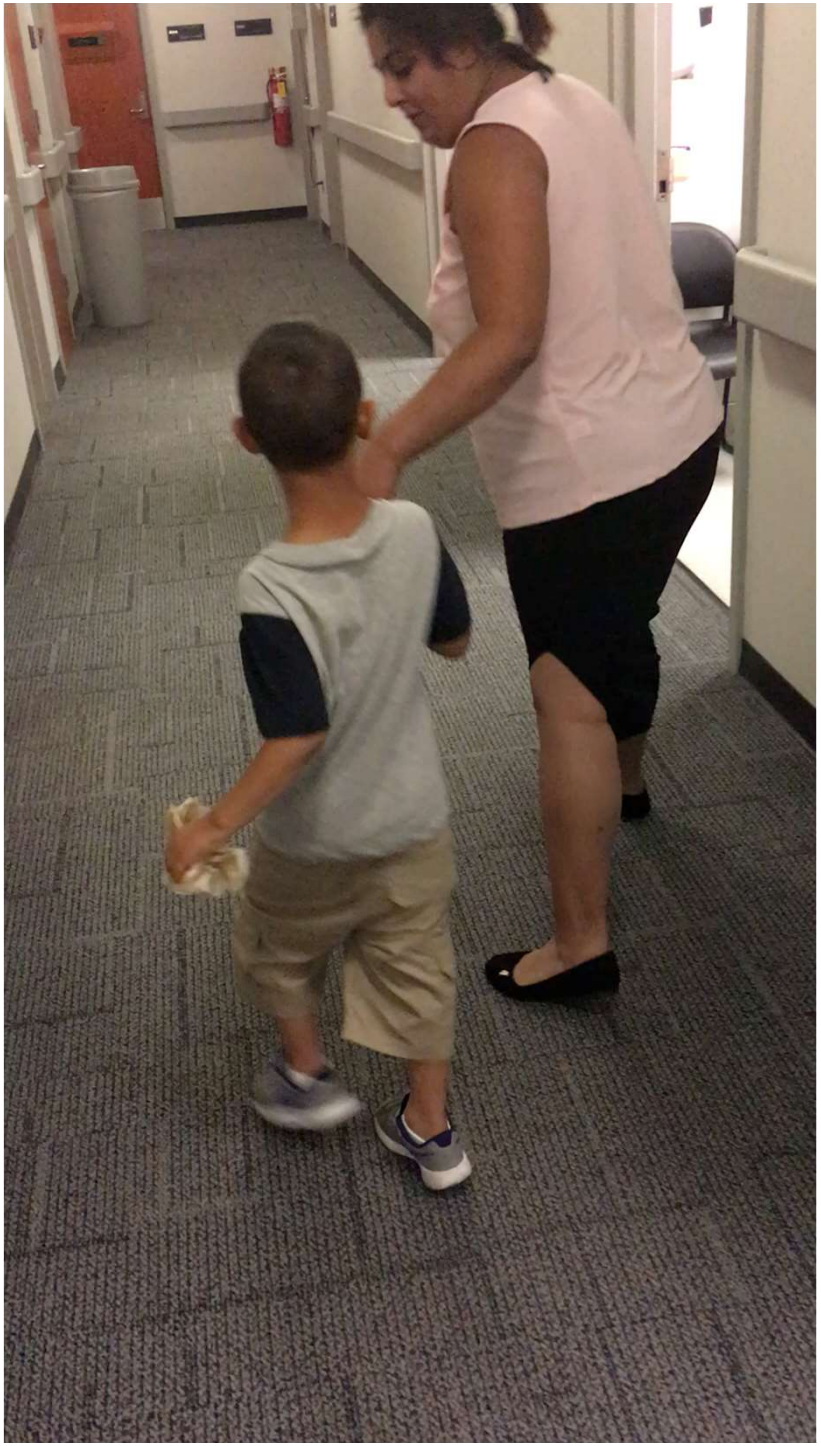
Family History: Father believes he may have a great cousin with drooping eyelids but does not know diagnosis. Maternal aunt with Hashimoto's thyroiditis

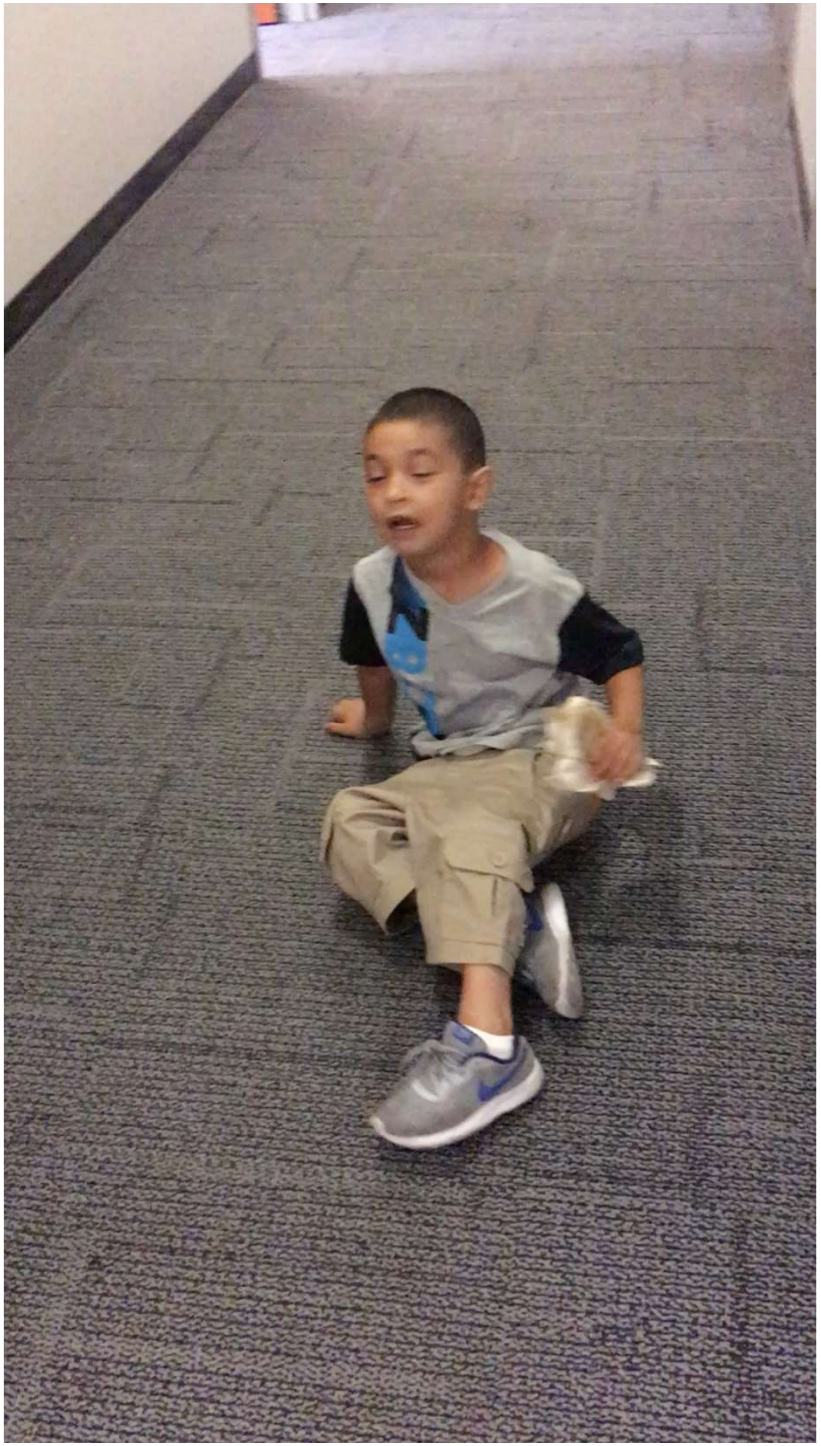
Social History: Lives at home with parents and older sister and older brother

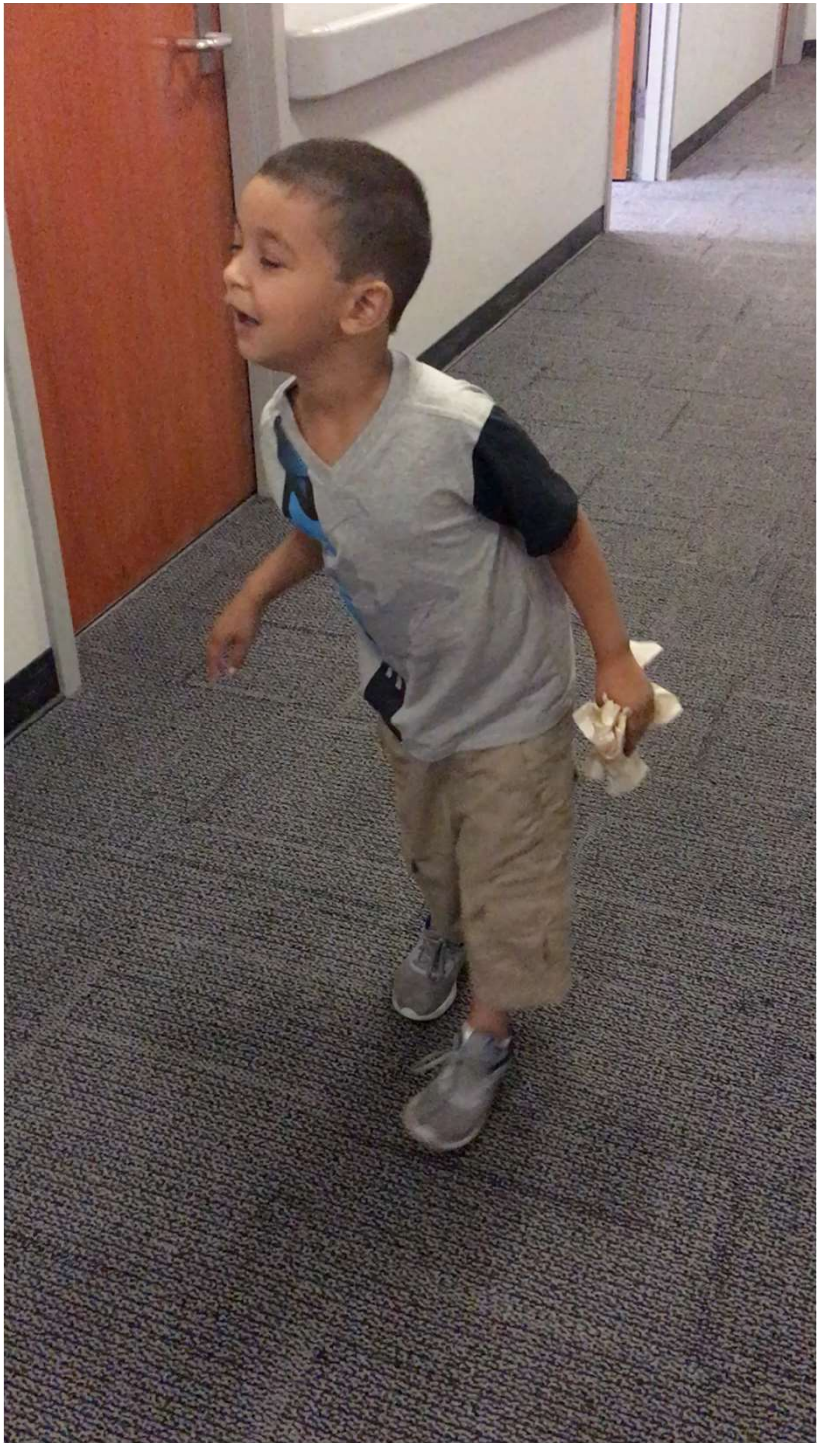
General Examination

- General: active young boy, in no apparent distress
- HEENT: bilateral ptosis, ophthalmoplegia, has large ears
- Cardiovascular: regular rate and rhythm, normal s1 and s2, no murmurs
- Respiratory: unlabored, clear to auscultation bilaterally
- Abdomen: soft, NTND, +BS
- Extremities: warm and well perfused
- Skin: no rashes or neurocutaneous lesions









Neurologic Examination

- **Mental status:** minimally verbal, will say single words with a soft, hoarse voice

- **Cranial nerves:**
  - Bilateral symmetric ptosis covering >75% of the eyes,
  - Pupillary responses brisk 5->2 bilaterally.
  - ophthalmoplegia with minimal eye movements in all directions
  - Facial strength mildly weak bilaterally with tenting of the mouth and drool present.
  - Facial sensation intact grossly.
  - Tongue normal

- **Sensory:** Reacts to light touch throughout.

Neurologic Examination

- **Motor:**
  - Reduced tone in limbs
  - Able to lift all extremities antigravity, however gives minimal resistance to examination.
  - Uses arms to get up from floor (modified Gower).
- **Reflexes:** 2+ throughout, Plantar responses – flexor bilaterally.
- **Coordination:** normal
- **Gait:** mildly lordotic, lurches forward to walk, mild foot drop.

Prior Workup

- CK - 140
- AchR Ab binding, blocking, modulating - normal
- Lactate/Pyruvate - normal

Differential Diagnosis?

Repetitive Nerve Stimulation

- 3 Hz RNS but at left peroneal-EDB was technically difficulty demonstrated a possible decrement

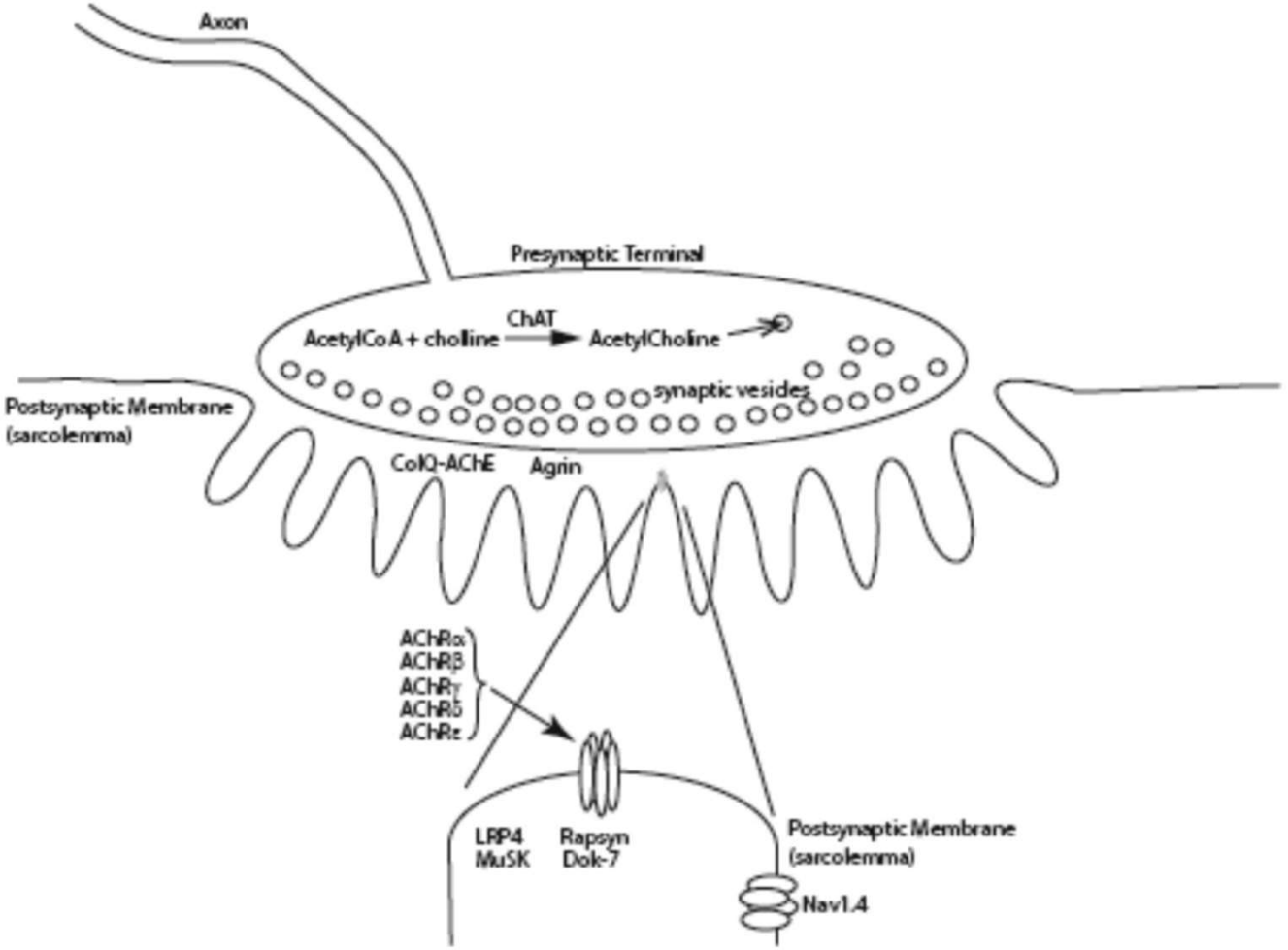
Genetic Testing

- The patient's family stated that they were from Italy, although they spoke a language that was clearly not Italian – Roma?
- Cognition may possibly be related to consanguinity
- Suspicion for Congenital Myasthenic Syndrome
- Sent genetic testing for CMS associated with Roma

Genetic Testing

- Homozygous for c. 1327del (p.Glu443Lysfs*64) in CHRNE gene
- Encodes epsilon subunit of Ach receptor resulting in frame shift
- This mutation has been described in the Roma population

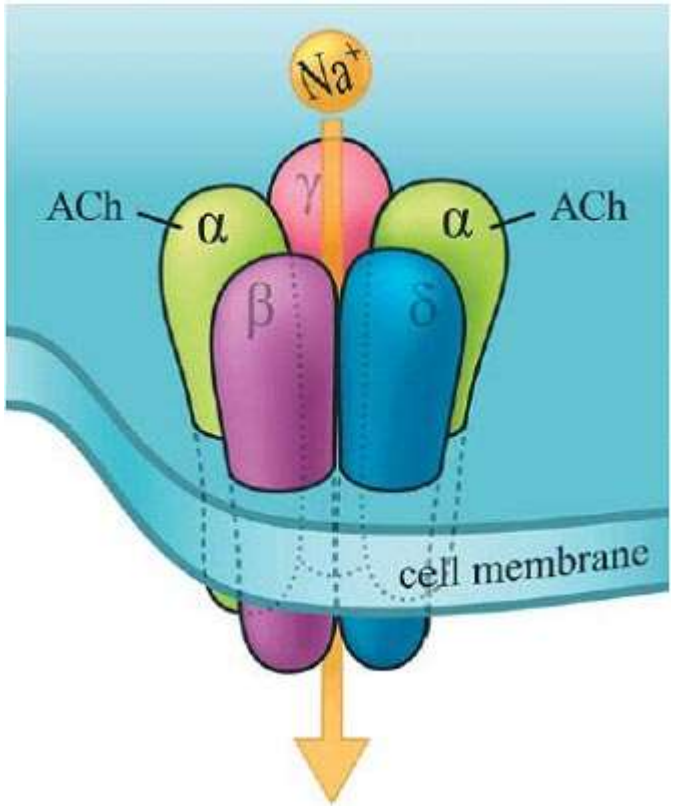
Overview of CMS



Congenital Myasthenic Syndromes classified by location of the defective protein

Acetylcholine Receptor

- Pentamer made of subunits alpha, beta, delta, gamma, epsilon
- Adult form consists of alpha x 2, beta, delta, epsilon
- Fetal form has gamma subunit rather than epsilon
- Mutation in epsilon subunit does not lead to complete loss of AChR due to persistent expression of fetal gamma subunit



Post-Synaptic AChR Syndromes

- AChR Deficiency due to null mutations in epsilon subunit, autosomal recessive
- Fast Channel Syndrome - hypoactive mutation, autosomal recessive
- Slow Channel Syndrome - Mutations that activate the channel, autosomal dominant

Figure 3A

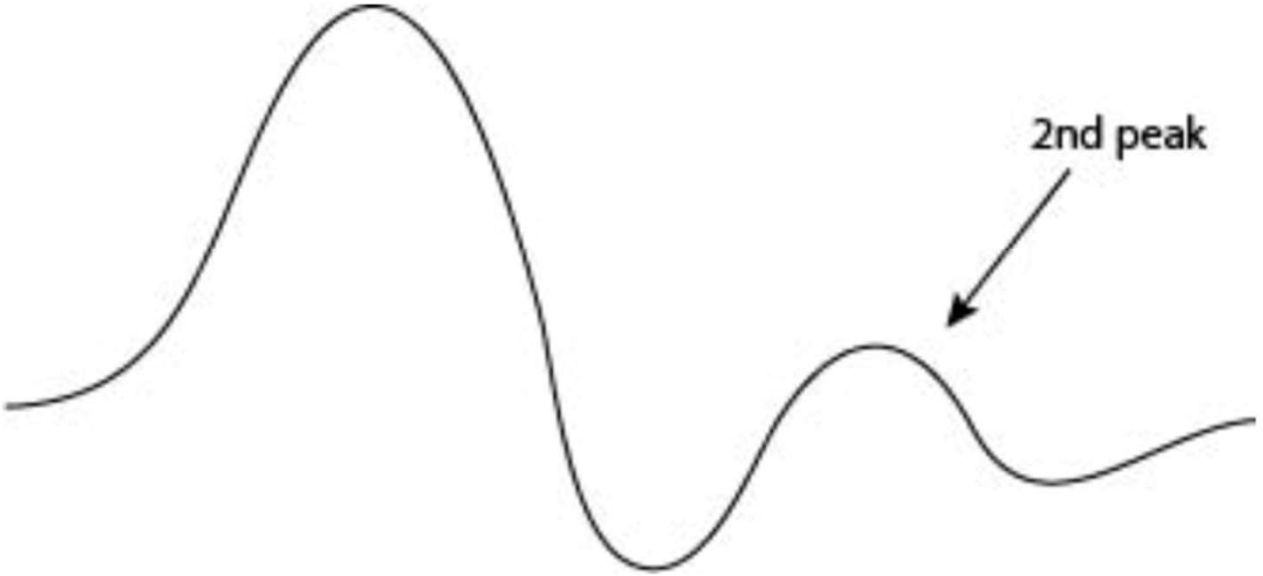
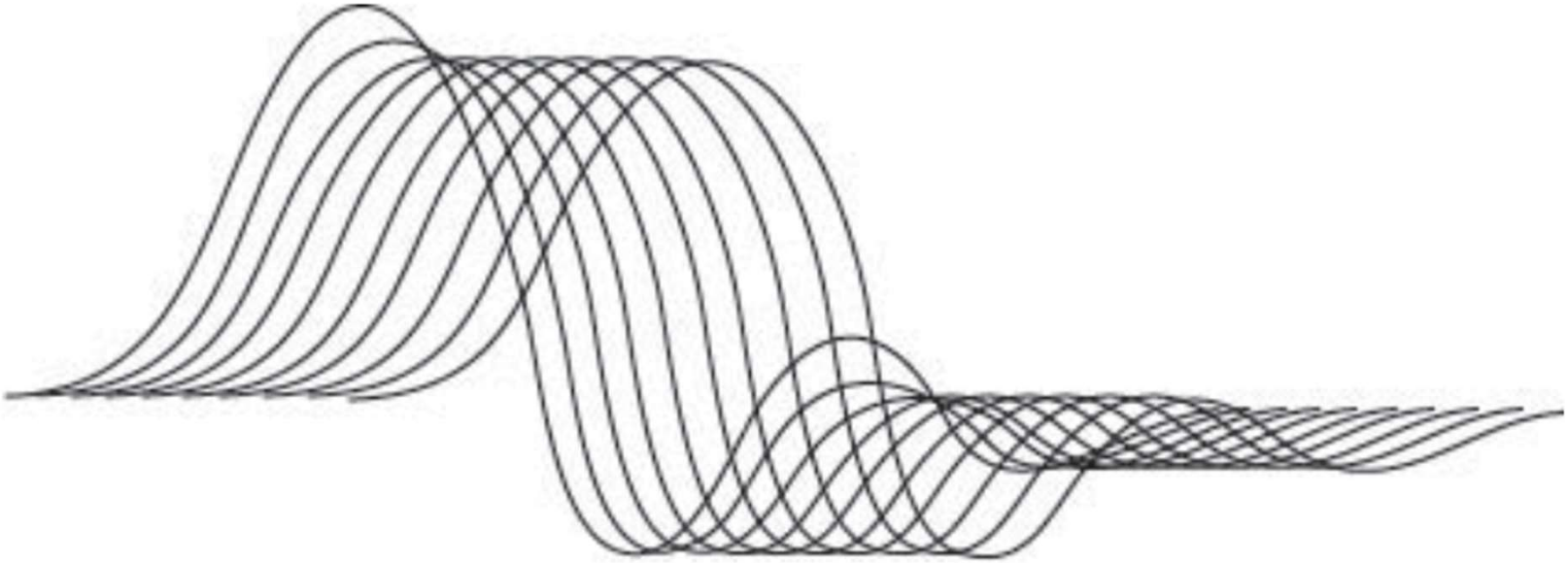


Figure 3B



CMS Summary

Location	Syndrome	Inheritance	Treatment	Comments
Pre-synaptic	ChAT	Recessive	AChE Inhibitor	Consider Ventilator & Apnea monitor
Synaptic	ColQ	Recessive	β-agonist	AChE Inhibitors contraindicated
Post-Synaptic	AChR Deficiency	Recessive	AChE Inhibitor, 3,4-DAP	consider β-agonist
	Slow Channel	Dominant	Fluoxetine, Quinidine	AChE Inhibitors contraindicated
	Fast Channel	Recessive	AChE Inhibitor, 3,4-DAP	
	Dok-7	Recessive	β-agonist	AChE Inhibitors contraindicated
	Rapsyn	Recessive	AChE Inhibitor, 3,4-DAP	consider β-agonist
	GFPT1	Recessive	AChE Inhibitor, 3,4-DAP	

Our Patient

- Started on pyridostigmine 30 mg q 4 hours as needed
- Decreased number of falls
- Rising from floor without use of hands
- Ptosis markedly improved
- Subjectively improved swallowing ability

References

1. Engel AG, Shen XM, Selcen D et al. Congenital myasthenic syndromes: Pathogenesis, diagnosis, and treatment. Lancet Neurol 2015 14:420-434
2. Unwin N. Structure and action of the nicotinic acetylcholine receptor explored by electron microscopy. FEBS Lett. 2003; 555:91-95