Pearls & Oy-sters: The Myasthenic Double Humps

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Pearls

- Congenital myasthenic syndrome (CMS) is an important diagnosis to consider in an adult with both fixed and fatigable weakness.
- Repetitive compound muscle action potentials (CMAPs) or "double humps" on routine nerve conduction studies can be a clue in certain subtypes of CMS such as acetylcholine receptor (AChR) defect and acetylcholinesterase deficiency.
- Slow channel CMS is a subtype of CMS caused by an autosomal dominant gain of function mutation in the AChR, clinically characterized by cervical and distal weakness.

Oy-sters

- Failure to consider this diagnosis may delay diagnosis and cause harm to the patient.
- Identification of the genetic subtype has clinical importance due to variable or detrimental response to treatments.
- Treatment of slow channel CMS relies on decreasing the duration of AChR opening with agents such as fluoxetine and quinidine.

A 38-year-old woman presented for progressive weakness and fatigue. She initially experienced fatigable weakness after giving birth to her first child. Gradually she developed difficulty holding up her head at the end of a day. She also could not tolerate walking or standing for a long time. She denies droopy eyelids or double vision. She has tried to work outside the home in the past but states she has never been able to hold a job because of her fatigue.

The patient's developmental history is only significant for delayed walking (age 2 or 3 years old). Her family history is notable for a brother and 2 cousins who carry the diagnosis of seronegative myasthenia gravis and a 3-year old daughter with genetically confirmed CMS. Her 8-year old son does not carry a genetic mutation for CMS.

The patient's physical examination revealed mild ptosis at rest in primary gaze and symmetrical mild to moderately limited extraocular movements most prominent during horizontal ductions. A curtain sign was present bilaterally. She had mildly decreased excursion on smile and Medical Research Council grade 4 strength on neck flexion and extension. She had grade 4 weakness throughout her arms except on wrist and finger flexion. Her legs were full strength except grade 4 weakness on bilateral hip flexion. Her reflexes, sensation, coordination, and gait were all within normal limits.

The patient's laboratory workup up to this point was significant for a creatine kinase level of 57 U/L (normal); negative AChR binding, blocking, and modulating antibodies; and negative muscle-specific tyrosine kinase antibodies.

Routine motor and sensory nerve conduction studies of the right arm showed normal amplitude, latencies, and conduction velocities. Analysis of the median and ulnar motor wave forms demonstrated repetitive CMAPs (figure). Repetitive nerve stimulation (RNS) revealed decremental response at 1, 2, 3, and 5 Hz. The repetitive CMAP abolishes with increasing RNS frequency (figure).

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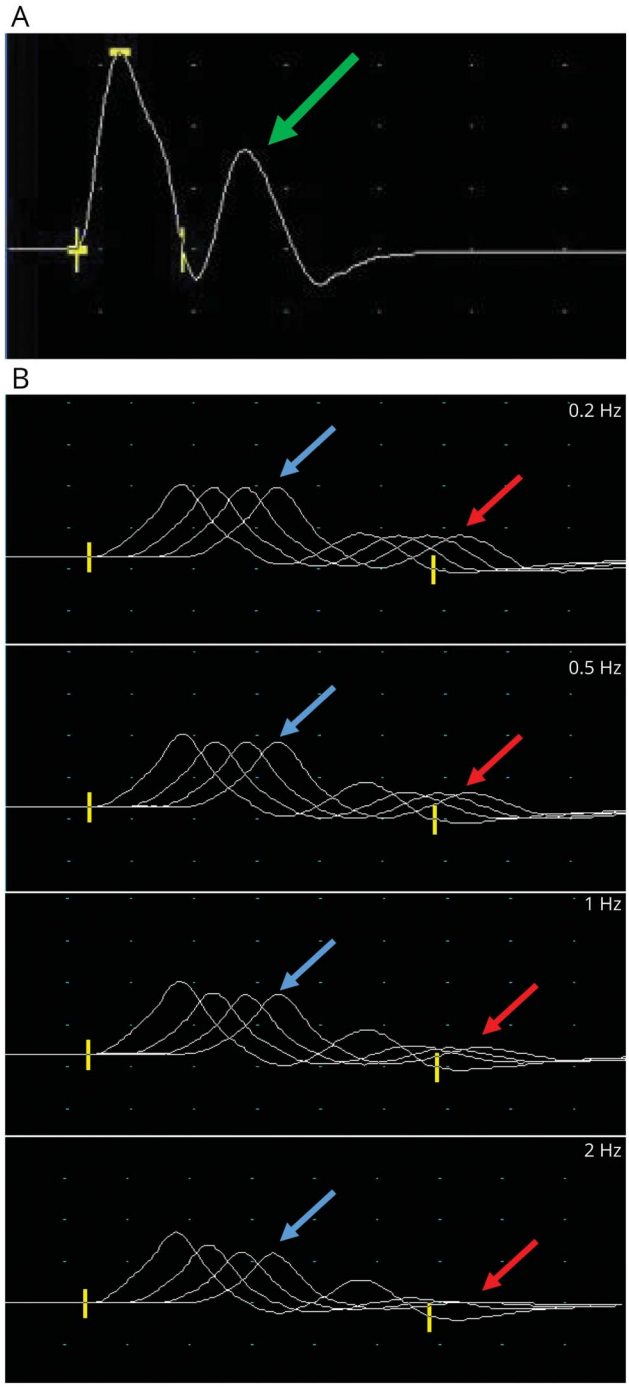
Figure Characteristic Repetitive Compound Muscle Action Potential (CMAP) and Abolishment With Repetitive Nerve Stimulation



(A) Single stimulus applied to the median nerve at the wrist (shown) evokes a repetitive CMAP (green arrow). (B) Repetitive nerve stimulation of the ulnar nerve at increasing frequencies to 0.2, 0.5, 1, and 2 Hz demonstrates decrement of the primary CMAP (blue arrows) and abolishment of the repetitive CMAP (red arrows) in higher frequencies.

Genetic panel testing confirmed a pathogenic variant in the *CHRNB1* gene (c.865G>A), which is the same genetic variant carried by the patient's daughter. This abnormality causes a slow-channel myasthenic syndrome due to a mutation in the β-1 subunit of AChR. The patient was prescribed fluoxetine for treatment of her condition and has plans to start this soon.

Discussion

CMS are a heterogeneous group of disorders caused by genetic defects in the proteins involved in neuromuscular junction structure, function, and repair.[1]

CMS can be caused by presynaptic, synaptic, or postsynaptic dysfunction. The most common CMS are the postsynaptic forms, and specifically those due to mutations in the genes encoding subunits of the muscle nicotinic AChR, causing kinetic changes that can be classified as either fast-channel or slow-channel syndromes. As was the case in this patient, slow-channel CMS is an autosomal dominant gain-of-function mutation in the AChR that causes a prolonged decay of the synaptic current.[2] This prolonged open time of the AChR results in entry of calcium ions into the muscle fiber, resulting in an endplate myopathy.[3]

CMS are misdiagnosed initially in the majority of patients and can take decades from onset of symptoms to correct diagnosis.[4] Clinically, in addition to fatigable weakness, a clue to the diagnosis of slow-channel CMS is the selective involvement of the cervical and forearm extensor muscles with asymmetric weakness after exercise.[3,5] Patients with advanced stage disease may have progressive weakness, muscle atrophy, ptosis, and ophthalmoplegia. The progression is thought to be gradual and symmetric. The onset varies from birth to middle age.[6] On electrodiagnostic testing, a repetitive CMAP, which has also been referred to as a "double hump"[7] or "double CMAP," is characteristically seen. A repetitive CMAP can also been seen in other disorders such as CMS due to acetylcholinesterase deficiency, with excessive use of acetylcholinesterase-inhibiting medications such as pyridostigmine, and organophosphate poisoning.[8]

The importance of subtyping CMS is related to the appropriate treatment (table). Pertinent for this patient, the classic symptomatic treatment for autoimmune myasthenia gravis with pyridostigmine is contraindicated in slow-channel CMS. These patients instead symptomatically benefit from open-channel AChR blockers, such as fluoxetine and quinidine.[9] A 3-year prospective open-label study showed improvement in the clinical examination and on neurophysiologic studies after treatment of fluoxetine 80–120 mg/d.[9] Quinidine is also shown effective when serum levels reach a therapeutic range of 1–2.5 μg/mL.[10]

By keeping CMS in the differential for fixed and fatigable weakness, patients can receive the correct diagnosis earlier. Most importantly, an accurate diagnosis will prevent patients from receiving unnecessary therapies and instead will be started on appropriate treatment. With the advent and commercialization of genetic testing for neuromuscular disorders, this diagnosis may be more readily made than before.

Table Selected Congenital Myasthenic Syndrome (CMS) Subtypes, Causative Genes, and Treatments

Subtypes of CMS	Gene	Treatment
Presynaptic		
Choline acetyltransferase (ChAT) deficiency	*ChAT*	Pyridostigmine, 3,4-DAP
Synaptic		
Acetylcholinesterase (AChE) deficiency	*COLQ*	Ephedrine, albuterol; avoid AChE inhibitors
Postsynaptic		
Primary acetylcholine receptor (AChR) deficiency	*CHRNA*, *CHRNB*, *CHRBD*, *CHRNE*	Pyridostigmine, 3,4-DAP
AChR kinetic abnormalities		
Slow channel syndrome	*CHRNA*, *CHRNB*, *CHRND*, *CHRNE*	Quinidine sulfate, fluoxetine; avoid AChE inhibitors
Fast channel syndrome	*CHRNA*, *CHRND*, *CHRNE*	Pyridostigmine, 3,4-DAP
AChR complex defects		
Rapsyn deficiency	*RAPSN*	Pyridostigmine, 3,4-DAP, albuterol
Dok-7 deficiency	*DOK7*	Ephedrine, albuterol; may worsen with AChE inhibitors
MuSK deficiency	*MUSK*	Albuterol; variable response to pyridostigmine and 3,4-DAP
Agrin deficiency	*AGRN*	Ephedrine, 3,4-DAP
Voltage-gated sodium channel	*SCN4A*	Pyridostigmine, acetazolamide
Tubular aggregates/defects in glycosylation	*GFPT1*, *DPAGT1*, *GMPPB*, *ALG2*, *ALG14*	Pyridostigmine, albuterol
Plectin deficiency	*PLEC1*	Variable response to 3,4-DAP

Abbreviations: 3,4-DAP = 3,4-diaminopyridine; Dok-7 = downstream of tyrosine kinase 7; MuSK = muscle-specific tyrosine kinase.
Adapted from references 1, 3, and 5.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Brian Stephens, MD, MS	University of California, San Francisco	Concept, acquisition of data, and writing and revising of the manuscript
Min Kang, MD	University of California, San Francisco	Concept, acquisition of data, and writing and revising of the manuscript

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