Clinical Reasoning: A child with delayed motor milestones and ptosis

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SECTION 1

A 6-year-old boy was evaluated for delayed motor milestones and ptosis. He was born at term without complications. He walked at 14 months; he was slow in running, jumping, and climbing compared to his peers. He fatigued easily. He had early-onset (within the first 3 months) bilateral ptosis. Some members on the maternal side of the family (male and female) had varying degree of weakness and ptosis (details unknown as the mother migrated from her home country). On examination, the patient had fatigable

bilateral ptosis, horizontal and vertical ophthalmoparesis, facial weakness, nasal dysarthria, proximal muscle weakness (lower limbs > upper limbs), and neck flexor weakness. Tendon reflexes were preserved and sensory and cerebellar functions were normal.

Questions for consideration:

1. What is the differential diagnosis in this case?
2. What tests would you consider to help narrow your differential diagnosis in this case?

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Supplemental data
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SECTION 2

The differential diagnoses in this case are broad and most likely involve lower motor neuron disorders. Lower motor neuron unit includes anterior horn cells, peripheral nerves, neuromuscular junction (NMJ), and muscles. Anterior horn cell disorders (spinal muscular atrophy in children) can present with motor delays and proximal weakness but presence of ptosis, facial weakness, and preservation of tendon reflexes go against that diagnosis. Peripheral neuropathies seem unlikely given lack of distal weakness, preserved reflexes, and no sensory findings. There are several features that point to an NMJ disorder: oculobulbar weakness, prominent fatigability, and proximal limb weakness. Among the NMJ disorders, autoimmune myasthenia gravis (MG) and congenital myasthenic syndrome (CMS) should be considered. Insidious onset of symptoms presenting within the first year of life and

positive family history favors CMS.^{1,2} Myopathies associated with ptosis $\pm$ ophthalmoplegia include congenital myopathies, mitochondrial myopathies, myotonic dystrophy, and oculopharyngeal muscular dystrophy (does not present in children).³

Creatine kinase (CK) was normal. EMG showed normal motor and sensory responses. Repetitive nerve stimulation (RNS) could not be performed due to poor tolerance. Needle EMG showed myopathic motor unit potentials; there were no myotonic discharges. A muscle biopsy showed some variation in fiber size and prominent type 2 fiber atrophy. There was no evidence of mitochondrial pathology on muscle biopsy.

Question for consideration:

1. What further testing would you consider to obtain a diagnosis?

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SECTION 3

Based on normal CK, myopathic muscle biopsy, and EMG findings, a congenital myopathy was considered. Genetic testing for centronuclear myopathies (*MTM1*, *DYNM2*, *BINI1*) as well as *RYR1* gene and

mitochondrial DNA sequencing were negative. As there was no unifying diagnosis, whole exome sequencing was performed, which revealed homozygous mutation of acetylcholine receptor ϵ gene (*CHRNE*) confirming the diagnosis of CMS.

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SECTION 4

In retrospect, RNS could have provided diagnostic clues for NMJ disorder. The child was started on pyridostigmine, which was gradually titrated up to 7 mg·kg⁻¹·d⁻¹ in 4 divided doses. His muscle weakness stabilized, fatigue improved, and he was able to participate in gymnastics and play soccer. There was some improvement of ptosis, but ophthalmoplegia persisted.

DISCUSSION Congenital myasthenic syndromes are a group of rare disorders that are genetically heterogeneous, resulting from more than 20 gene mutations affecting the NMJ.¹ A brief review of the normal function of NMJ will help to better understand the pathophysiology of CMS. At the presynaptic terminal, acetylcholine (ACh) is formed from choline and acetyl CoA with the help of enzyme cholineacetyltransferase (ChAT) and packaged into synaptic vesicles. A nerve impulse triggers release of ACh into the synaptic cleft. ACh diffuses and binds to the AChR receptors clustered on the crest of the postsynaptic membrane. This results in opening of central ion channel pore leading to depolarization of the muscle membrane through voltage-gated sodium channels located at the bottom of postsynaptic junction folds. ACh dissociates rapidly and is cleared from the synaptic cleft via the enzyme acetylcholine esterase (AChE).

General overview of CMS. Clinical features. CMS typically presents at birth or early childhood. However, milder phenotypes can present later in life or are unrecognized.¹ CMS is a great mimicker (table e-1 at Neurology.org) and should always be considered when a child presents with oculobulbar or respiratory symptoms, hypotonia, gross motor delays, weakness of the limb and axial muscles, along with diurnal variation of symptoms and fatigability. It should also be considered in patients with seronegative MG with poor response to immunotherapy.

Electrophysiologic studies. Routine motor studies can show repetitive compound muscle action potentials (CMAPs) in AChE deficiency and slow channel CMS after single stimulus. On low frequency (2–3 Hz) RNS, most CMS demonstrate decrement with post-tetanic repair and fatigue. At subtetanic stimulation (10 Hz), most CMS demonstrate decrement after 1–5 minutes; however, in ChAT deficiency, decrement is evident after 5 minutes with very slow recovery.¹ Single-fiber EMG is the most sensitive technique, which shows increased jitter and blocking in CMS.²

Genetic studies. Single gene tests are useful if there is a characteristic phenotype, family history, and EMG findings. As there is considerable phenotypic overlap,

a commercially available panel of CMS genes may be most cost-effective. Whole exome sequencing is emerging as a powerful tool in the diagnosis of novel syndromes or undiagnosed cases.¹

Treatment strategies. Unlike autoimmune MG, there is no immunologic abnormality in CMS, so immunotherapies are not effective. The mainstay of therapy in most CMS is AChE inhibitor (pyridostigmine most commonly used), which prolongs the action of ACh at the endplate (typical daily dose: 7 mg·kg⁻¹·d⁻¹).² Pyridostigmine is contraindicated in AChE deficiency, slow channel syndrome, and may worsen symptoms in Dok-7 myasthenia.^{1,2} 3,4-Diaminopyridine (3,4-DAP) is a potassium channel blocker that acts on the presynaptic ending and increases release of ACh (maximum daily dose: 80 mg/d). Oral albuterol and ephedrine are β_2 agonists that improve neuromuscular transmission by stabilizing the postsynaptic membrane.² They are the mainstay of therapy in Dok-7 and AChE deficiency. Open-channel blockers (fluoxetine and quinidine) are effective in slow channel syndrome. Patients with CMS should be cared for in a multidisciplinary setting with a neuromuscular specialist, pulmonologist, gastrointestinal/nutrition specialist, genetic counselor, and physical/occupational therapist.

Common specific subtypes of CMS. Presynaptic. Choline acetyltransferase deficiency. The hallmark of this syndrome is development of sudden apneas in the first year of life, which can be triggered by infection or stressors or without any apparent reasons.^{1,2,4} Patients with severe phenotype may never breathe spontaneously and develop cerebral atrophy from hypoxemia.⁵ A characteristic electrophysiologic finding consists of marked decrement after subtetanic stimulation followed by slow recovery over 5–10 minutes.¹ Pyridostigmine is helpful; 3,4-DAP also gives symptomatic relief.² Patients with recurrent apneas should have apnea monitor and home ventilator therapy (table 1).⁶

Synaptic basal lamina. AChE deficiency. Due to enzymatic deficiency, ACh stays in the synaptic cleft for a prolonged time, leading to depolarization blockade.² Prolonged end-plate potentials cause excitotoxic myopathy.² Children typically present with severe weakness since early life. About 25% of children show delayed pupillary dilation following constriction to light.¹ EMG classically shows repetitive CMAPs after single stimulus.^{1,2,4} Treatment is with albuterol or ephedrine.² Pyridostigmine is contraindicated.¹

Postsynaptic. Postsynaptic mutations affecting AChR account for the majority of CMS.¹ AChR deficiency due to ϵ subunit (*CHRNE*) mutation is the most common subtype (as presented in this vignette).^{1,2} The ϵ subunit found in adult AChR replaces the γ subunit in fetal AChR. The high frequency of *CHRNE* mutations compared to other subunits is attributable to the

Table 1 Characteristic clinical and electrophysiologic features and treatment options of common congenital myasthenic syndrome (CMS) subtypes

CMS subtype	Site of defect	Characteristic clinical features	Electrophysiologic characteristics	Treatment
Choline acetyltransferase deficiency	Presynaptic	Sudden apneas	Marked decrement of CMAP amplitude after subtetanic stimulation followed by slow recovery	AChE inhibitors Apnea monitors ± home ventilator
Acetylcholine receptor deficiency due to ϵ subunit (<i>CHRNAE</i>)	Postsynaptic	Most common CMS		AChE inhibitors ± 3,4-DAP ± albuterol
Slow Channel syndrome	Postsynaptic	Autosomal dominant Selective cervical and distal upper limb involvement	Repetitive CMAPs after single stimulus	AChE inhibitors and 3,4-DAP contraindicated Fluoxetine and quinidine helpful
Acetylcholine esterase deficiency (<i>COLQ</i>)	Synaptic lamina	Delayed pupillary dilation (25%)	Repetitive CMAPs after single stimulus	Albuterol or ephedrine AChE inhibitors contraindicated
Dok-7 deficiency	Development and maintenance of endplate	Limb girdle phenotype Stridor in neonatal-infantile period		Albuterol or ephedrine AChE inhibitors worsen symptoms
Rapsyn deficiency	Development and maintenance of endplate	Arthrogryposis and other congenital malformations (1/3)		AChE inhibitors and 3,4-DAP

Abbreviations: 3,4-DAP = 3,4-diaminopyridine; AChE = acetylcholine esterase; CMAP = compound muscle action potential.

phenomenon of phenotypic rescue.¹ AChR in the postsynaptic membrane is reduced to about 10% of normal.¹ These children present with ptosis and feeding difficulties within the first year of life.² Ophthalmoplegia develops within the first year of life and is often fixed.^{1,2} These patients also have varying degree of limb weakness.¹ They usually do not experience acute crises and are stable in the long term.² They typically respond to pyridostigmine. 3,4-DAP and albuterol can be used as adjuvant therapies.^{2,7}

Kinetic defects in AChR. Slow channel syndrome. This is inherited as autosomal dominant, unlike other CMS, which are mostly autosomal recessive. An important clinical clue is selective involvement of the cervical and distal upper limb muscles with relatively mild ocular symptoms.^{1,2} The pathophysiology is prolonged ACh channel opening leading to desensitization blockade and cationic overload of the postsynaptic membrane. Pyridostigmine and 3,4-DAP are contraindicated; fluoxetine and quinidine are helpful.⁸

Fast channel syndrome. Fast channel syndrome is a severe form of CMS in which patients experience acute crises on a baseline severe generalized weakness.² Many patients require respiratory support and gastrostomy tube due to severe respiratory and bulbar muscle compromise. Pyridostigmine and 3,4-DAP are helpful but effects may decline after initial response.²

Endplate development and maintenance. Dok-7 deficiency. Dok-7 deficiency typically presents with a limb girdle phenotype mimicking myopathy.¹ It can present in

the neonatal-infantile period with stridor.² Patients respond well with albuterol or ephedrine. Pyridostigmine usually worsens symptoms.²

Rapsyn deficiency. Rapsyn deficiency presents as an early-onset form that is severe and late-onset form that is mild. Arthrogryposis and other congenital malformations occur in about one-third.¹ Pyridostigmine and 3,4-DAP are usually helpful.²

CMS is a rare but frequently underdiagnosed entity that is potentially treatable, so clinicians should be vigilant about this entity, as seen in our case.

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P. Ghosh reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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