Clinical Reasoning: A 14-year-old boy with fatigue and episodic worsening of weakness

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SECTION 1

A 14-year-old right-handed boy was evaluated for fluctuating weakness and fatigue. He had normal motor milestones. At age 3 years, it was first noticed that he was not able to keep up with other children and had difficulty running. When he was 9 years old, his symptoms progressed, with easy fatigability and frequent falls. One of the striking features of his weakness was day to day variability. Some days he would be able to perform most of his daily activities and some days he could barely walk. In addition, he had episodes of severe weakness following febrile or viral illness, where he would become wheelchair-dependent lasting for days to weeks. He had shortness of breath with fatigability and intermittent wheezing, which was initially diagnosed as asthma but conventional asthma therapy did not help. Eventually, ear, nose, and throat evaluation determined that he had stridor. He denied diplopia, difficulty swallowing, or sensory symptoms.

The patient's initial neuromuscular evaluation at age 3 was unrevealing. He was reevaluated at age 9 and had normal nerve conduction study with negative repetitive stimulation of the trapezius and abductor digiti minimi (ADM) muscles. Needle examination showed myopathic changes. He had negative acetylcholine esterase receptor binding, modulating, and blocking antibodies and MuSK antibodies. Empiric treatment with pyridostigmine worsened his symptoms. Two muscle biopsies of the right thigh at age 10 and 11 years were unremarkable except for mild variation in fiber size. He was given the diagnosis of

mitochondrial myopathy based on mitochondrial enzyme study on the second muscle biopsy showing deficiency of complex III and IV. His mitochondrial DNA analysis for deletions and mutations was negative. Empiric treatment with carnitine, coenzyme Q10, and riboflavin was ineffective.

We examined the patient after he had a sick day with severe weakness. He was unable to walk. His cranial nerve examination revealed mild bilateral ptosis, with normal extraocular movements. There was mild weakness of bilateral facial muscles and sternocleidomastoid muscles. He also was noted to have right scapular winging, high arched palate, and exaggerated lumbar lordosis with some scoliosis. On motor examination, he had moderate neck flexors weakness and symmetric proximal more than distal limb muscle weakness. There was no significant muscle atrophy, joint contractures, or laxity. Muscle tone was normal. Sensory examination was normal. Deep tendon reflexes were normal and plantars were flexor bilaterally.

This patient had fatigable muscle weakness with severe episodic weakness following febrile or viral illnesses. He had mild facial and proximal more than distal limb muscle weakness, but extraocular movements and bulbar muscles were spared. There was no sensory involvement and reflexes were intact. He did not have any cognitive symptoms.

Questions for consideration:

1. Where would you localize this process?
2. What would be your differential diagnosis?

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SECTION 2

Intact reflexes and absence of sensory signs or symptoms would argue against a neuropathic process. Absence of upper motor neuron signs and sphincter abnormalities made a spinal process unlikely. No fasciculation or muscle atrophy would argue against a lower motor neuron syndrome. The potential localization would either be in the neuromuscular junction or in the muscle itself.

Fatigable weakness and fluctuation of severity is a feature of neuromuscular transmission disorder.¹ The patient did not have any hypotonia or prominent facial or axial muscle weakness to suggest congenital myopathy and his muscle biopsy did not reveal any of the characteristic features of congenital myopathy such as central cores, central nuclei, nemalin rods,

or congenital fiber type disproportion. He did not have calf hypertrophy or markedly elevated creatine kinase (CK) as seen in muscular dystrophy. He also did not have any symptoms to suggest metabolic myopathy such as myalgia, muscle cramps, or high CK during the episodes of severe weakness. He did not have any characteristic mitochondrial features such as progressive external ophthalmoplegia, hearing loss, cardiac abnormalities, or ragged red fibers or cytochrome C oxidase–negative fibers on his muscle biopsy.² Absence of any electrolyte abnormalities with previous attacks goes against channelopathy such as hypokalemic periodic paralysis.

Question for consideration:

1. What would be the next best investigation?

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SECTION 3

In this scenario, most logical next step would be to repeat the electrophysiologic testing, especially repetitive stimulation. As the patient's ADM and trapezius muscles were involved, they were chosen for the repetitive stimulation study. Two-Hertz repetitive stimulation showed 13% consistent decrement of the ADM and 35% decrement of trapezius muscle. After brief exercise, there was repair of the decrement of the ADM muscle, but not of the trapezius muscle (figure). These findings were most consistent with a postsynaptic defect of neuromuscular transmission.¹ On EMG, there were diffuse

rapidly recruited short-duration, low-amplitude, polyphasic motor unit potentials.

Based on the electrophysiologic study and pattern of weakness in the presence of scapular winging, high arch palate, scoliosis, and lumbar lordosis, congenital limb-girdle myasthenic syndrome (CLGMS) was suspected.^{3,4} CLGMS should be considered in patients presenting with fatigable limb weakness with or without ptosis and negative serology for acetylcholine receptor and MuSK antibodies. Muscle biopsies are often nondiagnostic or show nonspecific changes. Diagnosis of CLGMS is challenging and often delayed due to its variable phenotype. Misdiagnosis as mitochondrial myopathy or limb-girdle muscular dystrophy or congenital myopathies is common.^{3,4}

Figure Repetitive nerve stimulation study

Two-Hertz repetitive stimuli show 13% consistent decrement of abductor digiti minimi (ADM) and 35% decrement of trapezius muscle. After brief exercise, there was repair of the decrement of the ADM muscle, but not of the trapezius muscle.

Question for consideration:

1. What are the common etiologies of CLGMS?

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SECTION 4

Etiologies for CLGMS include docking protein 7 (*Dok-7*) mutation, end plate acetylcholine esterase deficiency, and disorders of glycosylation such as familial limb-girdle myasthenia gravis with tubular aggregates (TA) due to glutamine fructose-6-phosphate transaminase 1 (*GFPT1*) mutation, dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosaminophosphotransferase 1 (*DPAGT1*) mutation, and mutation in α -1,3-mannosyl transferase (*ALG2*), UDP-N-acetylglucosaminyltransferase subunit (*ALG14*), and GDP-mannose pyrophosphorylase B (*GMPPB*).^{3–8}

Dok-7 interacts with MuSK, which is important for the clustering of acetylcholine receptors on the postsynaptic cleft. *Dok-7* deficiency presents with limb-girdle weakness with relatively lesser degree of facial and cervical muscle involvement. Fluctuation of weakness is common. Moreover, it is associated with stridor. Histopathology reflects type I fiber preponderance with type II fiber atrophy and mild myopathic changes. They typically do not respond or worsen with acetylcholine esterase inhibitor therapy.^{3,4}

Endplate acetylcholine esterase deficiency from mutation of collagen-like tail subunit presents with generalized muscle weakness, but ophthalmoplegia is usually absent. Some patients can have slowing of the pupillary light reflex and a single nerve stimulus evokes a repetitive compound muscle action potential response.³

Disorders of glycosylation of neuromuscular proteins and acetylcholine receptor subunits can also cause CLGMS. Mutations in *GFPT1* and *DPAGT1* cause familial limb-girdle myasthenia gravis with TA. Patients with *GFPT1* present with predominantly fatigable proximal muscle weakness with mildly elevated CK level, which can be mistaken for limb-girdle muscle dystrophy. Patients with *DPAGT1* present with fatigable proximal muscle weakness, although distal weakness can also be seen. Some patients can have intellectual disability and autistic features. Both *GFPT1* and *DPAGT1* have TA on the muscle biopsy.^{3,5,6} Patients with *ALG2* mutation present with diffuse weakness, proximal more than distal involvement, proximal joint contractures, and distal joint laxity. TA can be present on muscle biopsy. Patients with *ALG14* typically present at later age, with or without joint contractures, and TA is usually absent.⁷ Congenital myasthenia from *GMPPB* mutations presents with limb-girdle muscle weakness, affecting proximal limb muscles, lower more than upper limbs. Some patients can have muscle cramps. Higher CK level and dystrophic features on muscle biopsy are usually present.⁸

Finally, late-onset Rapsyn deficiency can also present with limb-girdle muscle weakness, with no ocular

involvement, but these patients typically have substantial foot drop.⁹

Considering all these differentials, *Dok-7* deficiency appeared to be the best fit for this patient, given the presence of stridor, recurrent episodic severe weakness, and absence of TA on muscle biopsy. Genetic testing revealed 2 pathogenic heterozygous mutations: c.1124_1127dupTGCC and c.1378dupC in exon 7 of the *Dok-7* gene.^{4,10}

How to treat this patient? Cholinergic agents are of uncertain benefit and can actually worsen the symptoms in *Dok-7* mutation, and therefore should be avoided. Albuterol 4 mg 1–3 times a day in adults, 2 mg 2–3 times a day in the age group of 6–12 years, and 0.1 mg/kg/d (maximum up to 2 mg) 3 times daily for children between 2 and 6 years have shown clinical response.^{3,10} The patient was started on albuterol 4 mg twice a day with marked improvement in his symptoms.

Congenital limb-girdle myasthenic syndrome can be a challenging diagnosis and should be included in the differential diagnosis of patients presenting with limb-girdle muscle weakness with fluctuation. The progressive nature of the symptoms and in some cases dystrophic features on the muscle biopsy or elevated CK, along with myopathic EMG changes, can be confusing and some of these patients can be misdiagnosed with muscular dystrophy, seronegative autoimmune myasthenia, or mitochondrial myopathy. Making the correct diagnosis in these patients is imperative to avoid unnecessary procedures such as repeated muscle biopsies and potentially harmful immunotherapy and to start appropriate treatment without delay.

AUTHOR CONTRIBUTIONS

Bhaskar Roy: study concept and design, analysis and interpretation of data, drafted the manuscript. Nizar Chahin: study concept and design, acquisition of data, critical revision of manuscript for intellectual content, study supervision.

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