

Clinical Reasoning: A child with muscle stiffness

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Section 1

A 10-year-old boy presented with muscle stiffness of all extremities. His symptoms typically began during the second or third period of his hockey games and were intermittent, resolving within minutes of cessation of activity. Otherwise, he was asymptomatic. He was able to play baseball and soccer without similar symptoms, and he and his family denied clear triggers such as cold, heat, or meals with high carbohydrates or potassium. He denied vision problems, facial weakness, dysphagia, dysarthria, dyspnea, orthopnea, cramping, and fasciculations. He also denied sensory changes and bladder or bowel dysfunction. His family history was notable for myotonia congenita in his father, who was genetically heterozygous in 2007 for the pathogenic c.1437_1450del variant in the *CLCN1* gene.¹ His father reported similar symptoms including stiffness exacerbated by physical exertion. His parents were specifically concerned that the patient had inherited the mutation from his father. On neurologic examination, the patient had eyelid myotonia and trace percussion myotonia in the right thenar eminence. Strength was 5/5 throughout, and deep tendon reflexes were 2+ and symmetrical in all 4 extremities. Muscle bulk and tone were normal, sensory examination was normal, and coordination was intact. The patient's father had grip and eyelid myotonia and muscle hypertrophy.

Questions for consideration:

1. What is the differential diagnosis?
2. What are the next steps in diagnosis?

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Section 2

The patient in this vignette presented with intermittent muscle stiffness during his hockey games and was found to have clinical myotonia, the failure of muscle relaxation following activation, suggesting a myotonic disorder.² Myotonic disorders can be divided into 2 broad categories: dystrophic and nondystrophic myotonias. Dystrophic myotonias are classically associated with fixed weakness, systemic disease, and dystrophic changes on muscle biopsy. Nondystrophic disorders lack the aforementioned characteristics, with myotonia being the primary disease manifestation (table).² As the patient had no fixed weakness or signs of systemic disease, nondystrophic myotonias were at the top of the differential, specifically autosomal dominant myotonia congenita due to his family history. Myotonia congenita is defined by a mutation in the *CLCN1* gene, which codes for a chloride channel.² However, myotonia congenita typically presents with stiffness that is worse after periods of rest, which was not consistent with his presentation.³

Paramyotonia congenita and potassium aggravated myotonia were also on the differential. Paramyotonia congenita is due to a mutation in the *SCN4A* gene, which codes for a sodium channel.² Potassium aggravated myotonia is also due to a mutation in the *SCN4A* gene; however, it is defined by sensitivity to potassium levels.² Both paramyotonia congenita and potassium aggravated myotonia are associated with eyelid myotonia, which our patient exhibited. Although less likely due to the patient's lack of detectable, fixed weakness, both myotonic dystrophy 1 and 2 were considered as there are mild forms characterized only by myotonia, cataracts, and frontal balding with preserved strength.³ After discussion with the family, a decision was made to pursue genetic testing for the *CLCN1* mutation. The patient tested negative for any pathogenic variant.

Questions for consideration:

1. What are possible explanations for the patient's genetic testing results?
2. What is the next step?

Table Myotonic disorders

Disease	Category	Inheritance	Gene	Triggers	Associated features
Myotonic dystrophy type 1	Dystrophic	AD	<i>DMPK</i> , CTG repeats	None	Distal weakness, muscle atrophy, cardiac conduction abnormalities, cataracts, endocrinopathies, frontal balding, cognitive involvement
Myotonic dystrophy type 2 (also called proximal myotonic myopathy)	Dystrophic	AD	<i>ZNF9</i> , CTG repeats	None	Proximal weakness, myalgias, cataracts, autoimmune disease
Myotonia congenita	Nondystrophic	AD (Thomsen); AR (Becker)	<i>CLCN1</i>	Rest	Stiffness, muscle hypertrophy, no systemic features
Paramyotonia congenita	Nondystrophic	AD	<i>SCN4A</i>	Activity, cold	Stiffness of hands and facial muscles, marked sensitivity to cold, no systemic features
Potassium aggravated myotonias	Nondystrophic	AD	<i>SCN4A</i>	Potassium, activity	Varies

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; DMPK = myotonic dystrophy protein kinase; SCN4A = sodium channel protein type 4 subunit α ; ZNF9 = zinc finger protein 9.

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Section 3

In light of this surprising result, 2 possibilities were considered: (1) this was a laboratory error or (2) the patient did not have *CLCN1*-associated myotonia congenita but had another myotonic disorder. Moving forward, the following options were considered: (1) attribute the negative result to a laboratory error and retest the patient for a *CLCN1* mutation; (2) repeat genetic testing in the father to confirm his diagnosis of autosomal dominant myotonia congenita; (3) perform electrodiagnostic testing, such as EMG, to assess for electrical myotonia or exercise testing for characteristic changes; or (4) pursue broad genetic testing in the patient for other myotonic disorders. The decision was made to retest the father with a myotonia and paramyotonia congenita panel, which included the *CLCN1* gene (associated with myotonia congenita) and the *SCN4A* gene (associated with paramyotonia congenita), as the original testing was conducted more than a decade prior and clinical understanding of genetic results has advanced. Clinical suspicion that the patient and his father had the same myotonic disorder remained high; the decision was guided by a desire to determine an accurate diagnosis for both individuals and to avoid patient discomfort associated with EMG. The father again tested positive for the pathogenic *CLCN1* mutation, but was also found to have a pathogenic variant of the *SCN4A* gene, consistent with autosomal dominant paramyotonia congenita. Based on the father's history, examination, and laboratory results, it is likely that the father had a single *CLCN1* mutation associated with autosomal recessive disease, making him a carrier, and was previously misdiagnosed as having autosomal dominant myotonia congenita. In addition, the *CLCN1* mutation the father carries is most commonly associated with autosomal recessive disease. Repeat genetic testing of the patient revealed that he, too, was positive for the pathogenic c.3472C>T variant of the *SCN4A* gene, confirming a diagnosis of autosomal dominant paramyotonia congenita.

Discussion

Myotonia is defined as an inability to relax muscle after contraction, often described by patients as muscle stiffness, and it tends to diminish with repeated contraction.⁴ In other words, myotonia improves with exercise. Myotonic disorders belong to 1 of 2 categories: dystrophic or nondystrophic. Dystrophic myotonic disorders, such as myotonic dystrophy type 1 and type 2, are characterized by progressive muscle atrophy, weakness, and abnormal muscle histology.⁴ In contrast, the nondystrophic myotonic disorders, including paramyotonia congenita and myotonia congenita, are not associated with significant atrophy or weakness at onset, nor do they have dystrophic muscle histology.⁴ If individuals with nondystrophic disorders develop significant weakness, it tends to affect proximal muscles of the lower extremities and occur later in life.²

Paramyotonia congenita is distinct from the other myotonic disorders in that it presents with paradoxical myotonia.

Paradoxical myotonia is exacerbated by repeated muscle contraction. Clinically, patients with paramyotonia often complain of stiffness that worsens with exercise and cold.³ Paramyotonia congenita is an autosomal dominant disorder caused by a mutation in the *SCN4A* gene, which codes for a subunit of the skeletal muscle voltage gated sodium channel.⁴ It may present as early as the first decade of life with paramyotonia that is exacerbated by exercise, cold, or fasting, among other things.⁴ It is also classically associated with eye closure myotonia.⁴

The cornerstone of treatment for nondystrophic myotonic disorders is avoidance of triggers.² Pharmacologic therapies are targeted towards symptomatic control and include quinine, mexiletine, procainamide, phenytoin, and tocainide.² Evidence is largely anecdotal; however, mexiletine was effective in reducing stiffness in patients with nondystrophic myotonic disorders in a randomized controlled trial.⁵

Our patient's presentation was consistent with paramyotonia congenita: stiffness exacerbated by playing hockey (in other words, by cold and exercise) and prominent eyelid myotonia. By definition, he was experiencing paramyotonia, not myotonia. Based on his father's diagnosis, a presumptive diagnosis of myotonia congenita was erroneously made. This case highlights the value and limitations of genetic testing in neuromuscular disorders. The American Association of Neuromuscular and Electrodiagnostic Medicine states that genetic testing is a valuable tool in the diagnosis, investigation, and monitoring of neuromuscular disorders.⁶ This is a correct but not foolproof diagnostic method, especially when single gene mutations are associated with both autosomal dominant and recessive disease, as is the case with myotonia congenita. Each patient's signs and symptoms should directly guide genetic testing. When unexpected results occur, it is critical to return to the patient's history and physical examination to reevaluate the appropriateness of the chosen test. Only then should laboratory error be considered as an explanation for the results and repeat testing be entertained to clarify the diagnosis.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Suzahn Ebert, BS	Wake Forest, Winston-Salem	Analyzed data, drafted manuscript
Michael Cartwright, MD, MS	Wake Forest, Winston-Salem	Collected data, revised manuscript

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