Clinical Reasoning: A 38-year-old woman with childhood-onset weakness

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SECTION 1

A 38-year-old woman presented to the neuromuscular clinic for evaluation of progressive muscle weakness. She was born full-term and had normal early developmental milestones. In elementary school she had difficulty with hop-skip and keeping up with her peers. At age 10 years, she was noted to be unable to fully extend her elbows and was walking on toes. In college, she manifested slowly progressive lower limb weakness resulting in difficulty climbing stairs. She would fatigue easily after walking short distances. Subsequently, she developed difficulty lifting objects. At age 31, she delivered a healthy full-term boy uneventfully. She did not have visual symptoms, ptosis, facial weakness, dysarthria, or paresthesias. She developed dysphagia for solids and dyspnea on exertion 3–4 years before presentation. Her medical history includes hypothyroidism and Achilles tendon release. There is no history of parental consanguinity; her parents,

2 siblings, and the 7-year-old son had no muscle weakness. Her examination revealed generalized muscle atrophy and no fasciculations or action/percussion myotonia. She had mild facial weakness (Medical Research Council [MRC] grade 4), moderate neck flexor muscle weakness (MRC grade 3), and moderate to severe symmetric proximal (MRC grade 2–3) and mild distal limb weakness (MRC grade 4). Tendon reflexes were absent; sensory examination was normal for all modalities. She had a waddling gait, elbow and ankle contractures, and rigid spine (figure 1). There was no distal joint hyperlaxity or skin rash. Previously performed genetic test for survival motor neuron protein (*SMN1*) was negative.

Questions for consideration:

1. What is the differential diagnosis to this point?
2. What testing would be helpful to narrow the differential?

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Figure 1 Patient photograph

Photograph shows diffuse muscle atrophy, elbow contractures, and limited ability to flex neck and trunk.

Supplemental data
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From the Department of Neurology, Mayo Clinic, Rochester, MN.

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SECTION 2

This patient presented with childhood onset of symmetrical progressive predominantly proximal weakness in the absence of sensory changes and autonomic symptoms. The localization in her case could involve anterior horn cells, motor nerve roots, neuromuscular junction, and muscles. Given the childhood onset of symptoms, acquired disorders are unlikely (inflammatory or infiltrative polyradiculoneuropathies, autoimmune disorders of the neuromuscular transmission such as myasthenia gravis or Lambert-Eaton myasthenic syndrome, inflammatory myopathies). An inherited neuromuscular disease is likely. The lack of affected family members does not exclude the genetic etiology of the disease.

Serum creatine kinase (CK) values were mildly elevated (271–300 U/L; normal <176 U/L). EMG showed myopathic motor unit potentials and sparse

fibrillation potentials in the proximal limb and thoracic paraspinal muscles. Sensory and motor nerve conduction studies and repetitive nerve stimulations at 2 Hz were normal. Muscle biopsy of the quadriceps (performed previously and reviewed at our institute) showed increased number of fibers harboring single or multiple internal nuclei, fiber splitting, and increased endomysial connective tissue. The above information helped to rule out neurogenic processes, such as disorders of the anterior horn cells, and neuromuscular junction transmission defects, such as congenital myasthenic syndromes.

Questions for consideration:

1. Based on these findings, what is the differential diagnosis?
2. What testing would you perform to clarify the diagnosis?

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SECTION 3

The clinical history and neurologic findings, elevated CK values, and EMG findings point to a myopathic process. The pattern of the weakness points to a limb-girdle phenotype. The differential is broad and includes various forms of limb-girdle myopathies, such as limb-girdle muscular dystrophies (LGMD type 1 and 2), congenital muscular dystrophies, and congenital myopathies. The additional clinical clues that help narrow the differential diagnosis in this case were the early onset of elbow contractures and the rigid spine. Myopathies that can present with early-onset elbow contractures include Emery-Dreifuss muscular dystrophy (EDMD)¹ and collagen type VI–related myopathies (Ullrich and Bethle-hem myopathy).² EDMD phenotype can develop from mutations in 6 different genes with an X-linked recessive inheritance (mutation in emerin, *EMD*; and four and a half LIM domain protein 1, *FHL1*) and autosomal dominant inheritance (mutations in lamin A/C, *LMNA*; nesprin-1, *SYNE1*; nesprin-2, *SYNE2*; transmembrane protein 43, *TMEM43*).¹ Rigid spine syndrome (RSS) is a neuromuscular phenotype characterized by marked limitation in flexion of the cervical and dorsolumbar spine.³ RSS can be the predominant clinical feature of a number of myopathies, most prominent being various forms of EDMD,¹ various forms of congenital myopathies, in particular myopathies due to mutations in se-lonoprotein N (*SEPN1*),⁴ collagen type VI–related myopathy,² and very rarely in Pompe disease.⁵ Our patient lacked distal joint hyperlaxity, follicular hyperker- atosis, and abnormal skin scarring, which are character- istic of collagen type VI–related myopathies.

The patient's cardiac workup included an EKG that showed normal sinus rhythm, first-degree A-V block, and nonspecific intraventricular conduction delay. Holter monitoring identified 2 brief episodes of atrial fibrillation lasting less than 1 minute, while echocardiogram revealed no evidence for cardiomyopathy. Biopsy of the deltoid muscle showed nonspecific active and chronic myopathic changes (figure e-1 on the *Neurology*® Web site at Neurology.org). There were no vacuolar changes or other structural abnormalities suggestive of any specific congen- ital myopathy (nemaline rods, cores, mini-cores, fiber type disproportion, or radial distribution of the myofibrils in association with the internalized nuclei). Immunore- activity for 2 epitopes of collagen VI and laminin B1 were preserved, pointing away from, although pathologically not excluding, a collagen VI myopathy. Video swallow demonstrated mild oropharyngeal dysphagia. Pulmonary function tests showed reduced maximal respiratory pres- sures (27%–30% predicted) and overnight oximetry showed intermittent oxygen desaturation up to 70%.

Based on clinical phenotype, sex, and cardiac rhythm disturbances, genetic testing for EDMD due to lamin A/C mutation was recommended, but declined by the

patient. Two years later, she had a left middle cerebral artery cardioembolic ischemic stroke and was found to be in atrial fibrillation. She underwent pacemaker place- ment. At that point, she was referred back to our clinic for additional investigations. *LMNA* sequencing (per- formed by a commercial laboratory) revealed a novel heterozygous variant c.811_819del9ins3. This variant is predicted to result in an in-frame alteration, consisting of deletion of 3 amino acids and insertion of a missense amino acid (p.Leu271_Asn273delinsThr). The amino acids affected by this deletion in the lamin A protein are all evolutionary conserved across species from human to chimp, nonprimate mammals, chicken, frog, and zebra- fish. The novel *LMNA* mutation has not been detected in more than 500 control subjects. In addition, a pre- viously reported missense mutation, p.Leu271Pro (c. c.812T>C), located in the region deleted in our patient, was observed in identical twin brothers with autosomal dominant Emery-Dreifuss muscular dystro- phy and cardiomyopathy.⁶ These observations support the pathogenicity of the novel *LMNA* mutation found in our patient.

DISCUSSION Our patient was diagnosed with autoso- mal dominant EDMD due to lamin A/C mutation. The lamin A and C proteins are intermediate filament proteins of the internal nuclear lamina and derive from alternate splicing of the *LMNA* gene.⁷ Mutations in the *LMNA* gene result in a broad spectrum of phenotypes affecting multiple tissues, including muscle. The *LMNA* myopathy can be phenotypically heterogeneous, mani- festing as (1) autosomal dominant EDMD2, character- ized by childhood onset of elbow, posterior cervical, and ankle contractures and progressive humeroperoneal weak- ness; (2) autosomal dominant LGMD1B; and (3) con- genital muscular dystrophy (MDCL), characterized by progressive generalized weakness, dropped head, and early contractures.⁸ In addition, *LMNA* mutations can cause dilated cardiomyopathy with conduction system defects, axonal peripheral neuropathy (CMT2B1), progeroid syn- dromes with systemic involvement, mandibuloacral dys- plasia, and insulin resistance with lipodystrophy.⁷

Early diagnosis of *LMNA*-related muscular dystro- phy can be challenging.⁸ Neck extensor involvement is a common clinical finding, presenting either as dropped head in those with early-onset disease or as cervical contractures or significant weakness in those with EDMD and LGMD phenotypes. Elbow contractures are early diagnostic clues in patients with EDMD phe- notypes (as noted in our patient) but in patients with MDCL and LGMD they usually appear late in the disease course.⁸ Muscle histopathologic findings in these disorders range from mild nonspecific myopathic changes to severe myopathic changes suggestive of muscular dystrophy. Therefore, clinical suspicion

for the disease should lead to *LMNA* testing, despite the subtle pathologic findings.

Cardiac manifestations in laminopathies range from rhythm and conduction defects, including atrial and ventricular arrhythmias, to dilated cardiomyopathy.⁹ Sudden death is the most frequently reported mode of death (46%) in both cardiac and neuromuscular phenotypes.⁹ Implantable cardioverter defibrillator (ICD) implantation is often effective in preventing lethal tachyarrhythmias.¹⁰ Pacemakers alone are not sufficient in preventing sudden death because of the ventricular arrhythmias. Therefore, early diagnosis of laminopathy is essential for proper treatment and prevention of fatal complications. Our patient received anticoagulation therapy and underwent pacemaker and ICD placement after she had a cerebral ischemic infarct and was found to be in atrial fibrillation. An earlier molecular diagnosis would have resulted in a closer cardiac follow-up and more aggressive cardiac care, which may or may have not prevented the cerebral stroke.

Because of the risk of potentially lethal cardiac complications, there should be a low threshold for *LMNA* sequencing in patients with undiagnosed congenital muscular dystrophy having neck extensor weakness and in patients with undiagnosed LGMD and nonspecific myopathic features.⁸ Monitoring of the respiratory status (sometimes requiring noninvasive ventilation, which our patient had) and scoliosis are also important in the management of these patients. Genetic counseling and cardiac evaluation are important for family members due to the risk of fatal cardiac arrhythmias even in asymptomatic individuals.

AUTHOR CONTRIBUTIONS

Dr. Ghosh: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Dr. Milone: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision.

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DISCLOSURE

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