Pearls & Oysters: HyperCKemia with limb-girdle weakness

Think beyond myopathies

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PEARLS

- X-linked spinal and bulbar muscular atrophy (SBMA, Kennedy disease) should be considered in the differential diagnosis of male patients with significant elevation of creatine kinase (CK), limb-girdle weakness, and hyporeflexia/areflexia.
- Elevated CK levels may precede the onset of clinical weakness.
- Diffuse neurogenic EMG findings coupled with reduced/absent sensory nerve action potentials are characteristic electrophysiologic features of SBMA.
- Chronic neurogenic changes are histologic hallmark on muscle biopsy; myopathic changes are usually mild but can occur.

OY-STERS

- Owing to wide variability of clinical phenotype, SBMA should be considered even in the absence of classical bulbar symptoms, fasciculations, and gynecomastia.
- Elevated CK and mild myopathic findings in muscle biopsy should not dissuade the clinician from considering SBMA.
- Common misdiagnoses of SBMA include amyotrophic lateral sclerosis (ALS), adult-onset spinal muscular atrophy (SMA), and limb-girdle myopathies.

PATIENT 1 A 69-year-old man presented to our neuromuscular clinic with a prior diagnosis of muscular dystrophy. At age 56 years, during a cardiac evaluation, he was found to have elevated CK, which remained persistently elevated (800–2,600 U/L). At age 60 years, he noticed proximal lower limb weakness that progressively worsened, leading to the use of a cane to ambulate. He then developed proximal arm weakness, dysphagia, and rhinolalia. His diagnosis of limb-girdle muscular dystrophy of undetermined type had been based on limb-girdle weakness, elevated CK, and myopathic changes on quadriceps muscle biopsy. Genetic testing for myotonic dystrophy type 2 was negative.

Sequencing of all exons and flanking intronic regions of the calpain-3, dysferlin, α -, β -, δ -, and γ -sarcoglycan genes was normal. Family history was negative for neuromuscular disorders. He did not have biological children. On examination, he had facial and tongue weakness, Medical Research Council (MRC) grade 3/5 proximal arm weakness, and 3/5 hip girdle and quadriceps weakness with spared distal limb strength. No spontaneous fasciculations were noted but contraction fasciculations of the muscles were observed during manual muscle testing. Tendon reflexes were hypoactive or absent; sensory examination demonstrated mild reduction to pain and vibration in the distal third of the legs. Gynecomastia and testicular atrophy were not noted. CK value was elevated at 1,421 U/L (normal <336). Nerve conduction studies (NCS) revealed reduced or absent sensory nerve action potential (SNAP) amplitudes of the upper and lower limb sensory nerves. EMG study demonstrated diffuse neurogenic changes in the cranial, cervico-thoracic, and lumbosacral segments with fibrillation potentials. Slides of the outside biopsy of the quadriceps muscle, reviewed at our institution, showed findings suggestive of a chronic neurogenic process (either histochemical fiber type grouping, clusters of highly atrophic fibers of either histochemical type overreactive for nonspecific esterase, and numerous scattered hypertrophic fibers). Myopathic changes were mild (few necrotic fibers, rare regenerating fibers, increased internalized nuclei, and fiber splitting) and thought to be secondary to the neurogenic process. Genetic testing for SBMA showed increased trinucleotide CAG repeats (43, normal ≤ 36 repeats) in the androgen receptor gene (*AR*) confirming the diagnosis of SBMA or Kennedy disease.

PATIENT 2 A 71-year-old man presented to our neuromuscular clinic with the diagnosis of coexisting chronic demyelinating polyradiculoneuropathy (CIDP) and polymyositis. He had 10-year history of slowly progressive proximal lower limb weakness that had worsened significantly in the last 2–3 years, causing difficulty walking and climbing stairs. Over the last year, he developed bilateral grip weakness and

dysphagia to solids. Additionally, he reported numbness in his feet for 2 years. His CK value was elevated at 1,100 U/L. The diagnoses of CIDP and polymyositis had been based on muscle and nerve biopsy findings at an outside institution. Initial treatment with IV immunoglobulins (IVIg) improved his fatigue but not his weakness. Following development of extensive rash from IVIg, he was treated with prednisone and methotrexate with no clinical improvement, but development of interstitial pneumonitis. On examination, he had mild-to-moderate facial and tongue weakness, MRC grade 4/5 proximal and symmetric upper limb weakness, 4/5 hand muscle weakness, 3/5 hip girdle, and 4/5 quadriceps muscle weakness with spared distal lower limb strength. No spontaneous fasciculations were present. Tendon reflexes were absent; sensory examination demonstrated pan-modality sensory loss in the distal third of the legs. Mild gynecomastia was noted. CK value was elevated at 534 U/L (normal <336). NCS revealed reduced/absent SNAP amplitudes in the upper and lower limbs. EMG demonstrated diffuse neurogenic changes in the cranial, cervico-thoracic, and lumbosacral segments without fibrillation or fasciculation potentials. We reviewed the outside muscle biopsy of the quadriceps muscle that showed chronic neurogenic changes, mild myopathic changes, and small collections of perimysial inflammatory cells especially at perivascular

sites (figure, A–C). Muscle biopsy of the pectoralis major, performed at our institution, showed chronic neurogenic changes (figure, D–F). Genetic testing confirmed the diagnosis of SBMA (42 CAG repeats in *AR*).

DISCUSSION SBMA (Kennedy disease) is an X-linked recessive, adult-onset (third to fifth decade of life) lower motor neuron disease, characterized by slowly progressive weakness, atrophy and fasciculations in the bulbar and limb muscles, and hyporeflexia or areflexia.¹ Associated neurologic symptoms include muscle cramps, tremor, and varying degrees of sensory loss.¹ Signs of androgen resistance (gynecomastia, erectile dysfunction, and reduced fertility), glucose intolerance, and diabetes mellitus are often present.¹ Recently, Brugada-like ECG abnormalities were also described in patients with SBMA.²

SBMA is caused by CAG-polyglutamine repeat expansion within the exon 1 of *AR*. Nine to 36 CAG repeats are present in normal subjects, while expanded CAG repeats (38–62) are observed in patients with SBMA.³

The diagnosis of SBMA is usually straightforward when an individual manifests all the classic symptoms and signs that help distinguish it from disorders with similar clinical or electrophysiologic features, such as

Figure Patient 2 muscle biopsy of quadriceps and pectoralis major

(A–C) Quadriceps, (D–F) pectoralis major. (A) Muscle fiber size variation, internalized nuclei, fiber splitting (arrow), and necrotic fiber (asterisk). (B) Large clusters of atrophic fibers (arrows; hematoxylin & eosin). (C) Perivascular inflammatory reaction in the perimysium (arrow; trichrome-stained section). (D) Hypertrophic muscle fibers and clusters of highly atrophic fibers (arrow; hematoxylin & eosin). (E) Grouping of histochemical fiber types (ATPase pH 4.3). (F) Atrophic fibers overreact for nonspecific esterase (arrow). Bar is 50 μ m for all panels except E.

SMA and ALS.⁴ The X-linked recessive inheritance of SBMA is also helpful for the diagnosis, though family history is apparent in only about 50%–68% of the cases.^{1,4} The main clinical distinction between ALS and SBMA is the absence of upper motor neuron involvement in SBMA. Predominant proximal or less commonly predominant distal weakness would favor the diagnosis of SMA (SMA3 and DSMA3, respectively). However, there is significant phenotypic variability in SBMA that may make the diagnosis difficult and delayed. Limb weakness may not be the initial symptom. Nonspecific neurologic symptoms like tremors, fatigue, and muscle cramps commonly precede limb-onset weakness; bulbar symptoms usually occur relatively late in the disease course.⁴

Though elevated CK level is commonly associated with myopathies, it can also occur in the setting of neurogenic disorders and can lead to the erroneous diagnosis of primary myopathy, as noted in our patients. HyperCKemia can accompany SBMA, ALS, SMA, or inherited neuropathies.^{5–7} In general, hyperCKemia in neurogenic disorders tends to be less than 10 times the upper limit of normal.⁵ A high percentage of patients with SBMA (80%–84%) have hyperCKemia.^{1,4,5} The CK elevation can also precede the onset of clinical symptoms by many years,⁸ as in patient 1. The pathogenesis of the hyperCKemia in neurogenic disorders is poorly understood. However, in the case of SBMA, significant progress has been made in understanding the myopathic component of the disease. It has been suggested that the hyperCKemia in SBMA signals a primary myopathic process due to failure of activation of muscle satellite cells as a result of expanded androgen receptor protein accumulation.⁹ A recent study has demonstrated the need of expression of the polyglutamine-expressing androgen receptor in muscle to reproduce the full spectrum of SBMA disease. This study proved that CNS expression of the mutated androgen receptor is not sufficient for the development of motor neuropathy in SBMA transgenic mice, and that muscle has a key role in the pathogenesis of SBMA.¹⁰

In a series of 28 patients with SBMA, 12 (43%) with elevated CK underwent muscle biopsies and were misdiagnosed with a myopathy.⁵ Slides from 10 muscle biopsies of patients with SBMA reviewed by the authors demonstrated predominant neurogenic changes. Varying degrees of mild myopathic changes were also present, consisting of an increased number of internalized nuclei, necrotic or regenerating fibers, fiber splitting, and minimal inflammation.

Electrodiagnostic studies are helpful to differentiate SBMA from myopathic disorders as EMG shows diffuse neurogenic changes in SBMA. The associated

reduced SNAP amplitude is another useful finding to discriminate SBMA from SMA or ALS in which upper motor neuron signs have not yet developed.^{1,4}

These 2 cases underscore the importance of integrating clinical features and serologic, electrophysiologic, muscle pathologic, and molecular findings in formulating the correct diagnosis. In adult male patients with CK elevation and a chronic motor neuron syndrome without upper motor neuron signs, genetic testing for SBMA should be strongly considered, even in the absence of positive family history and other classical features of gynecomastia or sensory or bulbar findings.⁴ Though SBMA is a progressive degenerative neuromuscular disorder, it is generally considered to be relatively benign, with little effect on survival. Therefore, despite the lack of cure for the disease, the correct diagnosis has a major impact on prognosis, in addition to allowing reliable genetic counseling and preimplantation diagnosis. Furthermore, the correct diagnosis would prevent complications from exposure to immunosuppressant therapy, as observed in patient 2 who had been diagnosed with polymyositis.

AUTHOR CONTRIBUTIONS

Partha S. Ghosh: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Rajat Lahoria: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Margherita Milone: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. Eric J. Sorenson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.

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