A case of very late onset spinobulbar muscular atrophy with normal creatine kinase

Joseph P. Conway MD, Sakhi Bhansali MBBS, Yuebing Li MD, PhD

Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Introduction

Spinobulbar muscular atrophy (Kennedy disease) was initially clinically characterized in 1968 as a slowly progressive form of X-linked spinal and bulbar muscular atrophy (SBMA).[1] Its etiology lies in the expansion of tandem CAG repeats in the first exon of the androgen receptor (AR) gene. The disorder typically manifests as a slowly progressive lower motor neuron (LMN) disease affecting primarily proximal extremity and bulbar muscles. Other manifestations include peri-oral fasciculations, postural tremor, and symptoms of mild androgen insensitivity such as gynecomastia (GM). Certain serum laboratory abnormalities, such as elevated creatine kinase (CK), can help distinguish SBMA from other motor neuron diseases such as amyotrophic lateral sclerosis (ALS).[2] The age of neurologic symptom onset is typically between 30-50 years of life.[3] While larger retrospective case studies have postulated the possibility of symptom onset in adolescence for SBMA,[4] there is significant heterogeneity in clinical presentation. Previous case series suggest that approximately 60% of this heterogeneity can be attributed to variation in CAG repeat length, with higher repeat numbers correlating with a younger age of onset and increased severity.[1] Other components contributing to variability may include environmental, genetic, or epigenetic factors.[2] In this report, we describe a case of SBMA with several atypical features: symptom onset in the 8th decade of life, normal serum CK level, and absence of signs of androgen insensitivity.

Case Description

An 83-year-old, right-handed Caucasian man with a past medical history notable for smoking, chronic obstructive pulmonary disease, and remote heavy alcohol consumption presented in the Spring of 2022 for evaluation of progressive dysphagia and weakness and atrophy in the muscles of all four extremities over the previous five years. His symptoms started initially with dysphagia, and he endorsed 40 lbs weight loss over a two-year period. He reported difficulty in gripping, using buttons and zippers, and recent difficulty holding his head up. In the year prior to presentation he developed progressive dysarthria, gait instability requiring use of a cane, diffuse muscle twitching and muscle atrophy in the bilateral arms, legs, and face.

His neurological exam had several notable findings such as tongue weakness and atrophy without fasciculations, diffuse muscle atrophy in the bilateral arms, legs, and face, and fasciculations in the perioral region and all four extremities. He had mild (4 to 4- on the Medical Research Council Scale) neck flexor weakness, symmetric proximal and distal upper extremity muscle weakness, and mild right more than left weakness in the proximal and distal muscles of the lower extremity (MRC 4/5 to 4-/5). All deep tendon reflexes were absent, and there were no pathological reflexes or frontal release signs elicited. No sensory or coordination abnormalities were appreciated aside from impaired tandem gait. Of note, there was no evidence of gynecomastia or reduced facial hair and he had no history of testicular atrophy or infertility.

Blood work including thyroid stimulating hormone, vitamin B12, folate, hemoglobin A1c, serum immunofixation, kappa/lambda free light chain assay, CK, complete blood count and comprehensive metabolic panel were unremarkable. MR imaging of the brain and cervical spine with contrast was largely unremarkable. On nerve conduction study sensory nerve action potentials (SNAPs) were diffusely absent in the left upper and lower extremities. Needle electromyography showed evidence of active denervation in the thoracic and sacral paraspinal muscles as well as in the distal upper and lower extremity muscles. Diffuse chronic neurogenic changes were observed in the cranio-bulbar, cervical, thoracic, lumbar and sacral regions. These findings were felt to be consistent with combinatorial diagnoses of a motor neuron disease (MND) such as ALS and a concurrent sensory or sensorimotor polyneuropathy secondary to excessive alcohol intake. The diagnosis of ALS was later called into question when his exam remained largely stable on a follow up visit several months later. He ultimately underwent genetic testing for androgen receptor (AR) repeat expansion, which returned positive for 40 repeat expansions of the AR gene consistent with a diagnosis of SBMA. [3]

Discussion

This patient presented with a slowly progressive LMN pattern weakness without significant sensory deficits on physical examination, but with findings on EMG suggestive of MND and concurrent sensory polyneuropathy. The differential diagnosis considered during his initial workup included slowly progressive LMN-predominant MND such as primary muscular atrophy (PMA), ALS, SBMA and chronic neurotoxic effects from remote heavy alcohol consumption. The patient's history of slowly progressive weakness and atrophy affecting facial, bulbar and limb muscles, LMN involvement with fasciculations, absent SNAPs on nerve conductions studies, and positive genetic

testing for 40 repeat expansions of the AR gene (normal number of repeats is 34 or fewer) were consistent with a diagnosis of SBMA.

SBMA is a genetic condition caused by a pathogenic repeat expansion of CAG nucleotides in exon 1 of the AR gene on chromosome Xq11-12.[4] Repeats of 38 or more follow complete penetrance.[5] The AR gene is a ligand-activated transcription factor with a steroid receptor structure. It mediates the physiological action of androgens in male sexual differentiation and spermatogenesis. Dysfunction of the AR receptor causes features of androgen insensitivity in males. Patients with SBMA frequently exhibit characteristics of partial androgen insensitivity, such as oligospermia/azoospermia and testicular atrophy, leading to infertility, gynecomastia, and/or reduced facial hair.[3] Female carriers of SBMA are usually asymptomatic due to low levels of circulating androgen though some may develop mild symptoms of intermittent muscle cramps or twitching.[1]

While the pathogenic mechanism remains incompletely understood, it is widely believed that accumulation of toxic expanded AR in the nucleus leads to degeneration of LMNs in brainstem nuclei and the spinal cord.[1,4] Symptoms of this condition include muscle weakness and atrophy, muscle cramping, gait impairment, fasciculations, dysphagia and dysarthria, and mild-to-moderate sensory abnormalities in the distal extremities.[5] Symptoms of SBMA tend to progress slowly over time, however patients with larger numbers or repeat expansions have been shown to progress more rapidly.[6]

This case of SBMA was atypical in four distinct ways: age at symptom onset being much later than typically occurring; lack of appreciable symptoms or examination findings of androgen insensitivity; and normal CK level. Symptoms of SBMA typically begin in adulthood (average onset of symptoms between 30-50 yo), but one case report of two Japanese twin brothers reported ages of onset as old as 66 and 78 years old. [7] The age of neurological symptom onset is inversely correlated with the number of AR repeat expansions, in that individuals with fewer repeat expansions may not develop symptoms until later in life.[1] The delayed onset in this case could be explained by his lower CAG repeat length.

On electrodiagnostic studies, KD often shows finding of diffuse axonal loss changes. In addition, SNAPs are often diffused reduced or absent, without a length-dependent pattern. Absent or diffusely low SNAP amplitudes without physical examination findings of significant sensory abnormalities is characteristic of the disease.[15]

CK level has been shown to be a valuable biomarker for SBMA for several reasons: elevated CK is seen in 84-94% of patients.[8,9] CK elevations are often at least 3 times the upper limit of normal.[12] CK levels are significantly higher in SBMA compared to healthy controls and ALS patients.[2] CK elevations are seen in SBMA due to muscle degeneration secondary to denervation as well as a primary myopathic process. [10,11]CK levels have been correlated with disease severity and have been shown to decrease in patients experiencing improved muscle symptoms while receiving treatment[11]However the value of CK as a marker of disease progression and stage is less clear.[3]

The management of SBMA is largely supportive. Patients benefit from multidisciplinary care involving occupational and physical therapy, speech and feeding therapies, and psychosocial support services for the patient as well as their caregivers. Consistent follow up is needed with specialists in neurology, cardiology, pulmonology, and endocrinology to monitor progression and potential complications of the disease. Consultation with genetics is helpful not only in confirming the diagnosis, but to counsel the patient and their family members regarding the implications of this genetic mutation. Many therapies aimed at reducing levels of toxic AR protein are being investigated for future use.

In summary, neurologists should suspect SBMA in male patients with LMN-pattern muscle weakness, areflexia, elevated serum CK levels, and signs of androgen insensitivity. However, this case provides further evidence of the clinical heterogeneity and potential difficulty in diagnosing this disease; onset of neurologic symptoms may occur much later in life than initially described, CK levels may be normal, and there may be an absence of androgen insensitivity signs. Furthermore, EMG findings may lead one to suspect ALS or other forms of MND and may be confounded by a clinical history suggestive of sensory polyneuropathy.

References

1. La Spada A. Spinal and Bulbar Muscular Atrophy. 1993. PMID: 20301508

2. Lieberman AP, Yu Z, Murray S, Peralta R, Low A, Guo S, Yu XX, Cortes CJ, Bennett CF, Monia BP, La Spada AR, Hung G. Peripheral Androgen Receptor Gene Suppression Rescues Disease in Mouse Models of Spinal and Bulbar Muscular Atrophy. Cell Rep. 2014 May;7(3):774–784. PMID: 24746732

3. Hashizume A, Fischbeck KH, Pennuto M, Fratta P, Katsuno M. Disease mechanism, biomarker and therapeutics for spinal and bulbar muscular atrophy (SBMA). J Neurol Neurosurg Psychiatry. 2020 Oct 15;91(10):1085–1091. PMID: 32934110

4. Finsterer J. Perspectives of Kennedy's disease. J Neurol Sci. 2010 Nov;298(1–2):1–10. PMID: 20846673

5. Breza M, Koutsis G. Kennedy's disease (spinal and bulbar muscular atrophy): a clinically oriented review of a rare disease. J Neurol. 2019 Mar 13;266(3):565–573. PMID: 30006721

6. Igarashi S, Tanno Y, Onodera O, Yamazaki M, Sato S, Ishikawa A, Miyatani N, Nagashima M, Ishikawa

Y, Sahashi K, Ibi T, Miyatake T, Tsuji S. Strong correlation between the number of CAG repeats in androgen receptor genes and the clinical onset of features of spinal and bulbar muscular atrophy. Neurology. 1992 Dec 1;42(12):2300–2300. PMID: 1461383

7. Hemmi S, Inoue K, Kutoku Y, Rikimaru M, Murakami T, Sunada Y. Two brothers with very late onset of muscle weakness in X-linked recessive spinal and bulbar muscular atrophy. Rinsho Shinkeigaku. 2009;49(1):22–26. PMID: 19227892

8. Querin G, Bertolin C, Da Re E, Volpe M, Zara G, Pegoraro E, Caretta N, Foresta C, Silvano M, Corrado D, Iafrate M, Angelini L, Sartori L, Pennuto M, Gaiani A, Bello L, Semplicini C, Pareyson D, Silani V, Ermani M, Ferlin A, Sorarù G. Non-neural phenotype of spinal and bulbar muscular atrophy: results from a large cohort of Italian patients. J Neurol Neurosurg Psychiatry. 2016 Aug;87(8):810–816. PMID: 29898093

9. Chahin N, Sorenson EJ. Serum creatine kinase levels in spinobulbar muscular atrophy and amyotrophic lateral sclerosis. Muscle Nerve. 2009 Jul 16;40(1):126–129.PMID 19533663

10. Lombardi V, Querin G, Ziff OJ, Zampedri L, Martinelli I, Heller C, Foiani M, Bertolin C, Lu CH, Malik B, Allen K, Rinaldi C, Zetterberg H, Heslegrave A, Greensmith L, Hanna M, Soraru G, Malaspina A, Fratta P. Muscle and not neuronal biomarkers correlate with severity in spinal and bulbar muscular atrophy. Neurology. 2019 Mar 12;92(11). PMID: 30787165

11. Cai BC, Zhong LF, Liu YH, Sui ZY, Yang Q, Zeng DT, Li X, Xu WD, Chen T. Genotype and clinical phenotype analysis of a Family with Kennedy disease. Medicine. 2023 Apr 14;102(15):e33502.PMID: 37058074