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From sarcopenia to a genetic diagnosis: Exercise-induced weakness and androgen insensitivity unmasking Kenedy's disease

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Abstract

Spinal and bulbar muscular atrophy, or Kennedy's disease, is a rare, X-linked neurodegenerative disorder often misdiagnosed due to its mimicry of common musculoskeletal conditions. Diagnostic delay is typical, averaging five years. A 46-year-old male presented with a three-year history of progressive, exertional lower limb weakness and buttock pain following a minor fall. Extensive evaluations for lumbosacral radiculopathy, piriformis syndrome, peripheral arterial disease, and tendinopathy were unremarkable. Key examination findings included subtle fasciculations, and hyporeflexia, with absent of obvious atrophy. Serial bioimpedance analysis objectively demonstrated an inability to accrue skeletal muscle mass despite dedicated rehabilitation. The critical diagnostic inflection point was the recognition of previously overlooked signs of androgen insensitivity: gynecomastia and long-standing erectile dysfunction with retrograde ejaculation. This constellation of findings prompted genetic testing, which confirmed a pathologic CAG repeat expansion (48 repeats) in the androgen receptor (AR) gene. This case underscores that in males with progressive lower motor neuron symptoms, the presence of endocrine features even subtle or long-standing is paramount to distinguishing spinal and bulbar muscular atrophy from its mimics. Unexplained, exertional weakness with objective evidence of neurogenic atrophy on body impedance analysis should elevate clinical suspicion. A holistic review of systems and signs is essential to shortening the diagnostic odyssey in rare neurological diseases.

Keywords: Sarcopenia, neurology, exercise

INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a rare X-linked recessive disorder caused by a CAG trinucleotide repeat expansion in the androgen receptor (AR) gene.[1] This results in a toxic gain-of-function protein with an expanded polyglutamine tract, leading to progressive degeneration of lower motor neurons and dorsal root ganglia. The estimated prevalence 1 in 40 000, contributing to frequent misdiagnosis.[2] The classic triad of SBMA includes progressive limb and bulbar weakness, fasciculations, and signs of partial androgen insensitivity, such as gynecomastia, reduced fertility, and erectile dysfunction. However, initial presentations are often atypical, focusing on isolated musculoskeletal complaints, which leads to extensive and unnecessary investigations.

This case report details an atypical presentation of SBMA dominated by exertional weakness in the absence of overt bulbar signs. The objectives of this report is to describe an atypical case of Kennedy's disease presenting with predominant exertional weakness and to illustrate how the integration of neuromuscular findings with endocrine features and objective body composition data can resolve a prolonged diagnostic dilemma.

CASE REPORT

A 46-year-old male was referred to Sports Medicine clinic in January 2023 for evaluation of exertional radiating left buttock pain and bilateral lower limb weakness. His symptoms

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began insidiously in 2020 following a minor fall. Prior to our assessment, he had undergone a multi-specialty evaluation. Orthopaedic spine services, upon finding only normal finding on lumbosacral MRI without nerve root compression (Figure 1(a)), and normal hip MRI without any enlargement over piriformis muscle (Figure 1(b)), nor any sciatic nerve compression, and discharged him. He was referred to physiotherapy for radicular pain and piriformis syndrome, compliance with physiotherapy without any improvement. Vascular surgery ruled out peripheral arterial disease with bilateral lower limb CT angiography and normal ankle-brachial indices. Neurological consultation noted diffuse subtle fasciculations but, in the absence of upper motor neuron or bulbar signs, did not initially pursue motor neuron disease and was discharge from neurology clinic.

Initial examination in our clinic revealed appendicular muscle mass of 4.7 kg.m^2, hand grip strength of 20kg, but his walking speed is 1m/s. There is a subtle steppage gait only seen after prolong walking, diffuse subtle fasciculations in the limbs and torso, and hyporeflexia. The working diagnosis remained sarcopenia due to deconditioning. The patient adhered to a structured strengthening rehabilitation program comprises of resistance cycling, progressive compound resistance exercise of upper and lower limb, with increased caloric and protein intake. Despite this, serial bioimpedance analysis (Table 1) over 18 months consistently revealed a persistently low and stagnant skeletal muscle mass, objectively contradicting the expected trajectory of a primary musculoskeletal or deconditioning syndrome.

The diagnostic turning point occurred in late 2024. During a routine follow-up, closer physical examination revealed bilateral gynecomastia. Directed history-taking uncovered a long-standing history of erectile dysfunction with

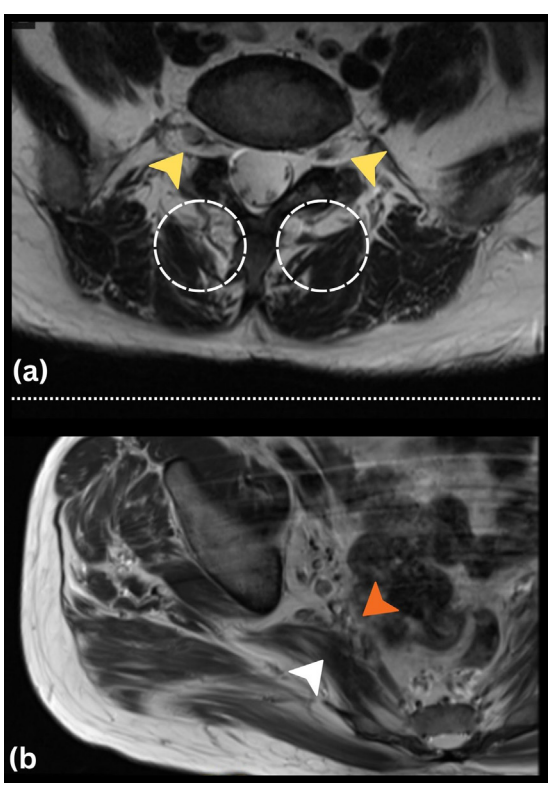

Figure 1. (a) show an MRI image axial T2 weighted image of L4-L5 region. Note that there is preserved foraminal space (yellow arrow head) with no impingement at L4 and L5 nerve root. Noted mild atrophy over bilateral multifidus (white circle). Figure 1(b) showed MRI image of left hip in axial view, showing normal bulk piriformis (white arrow head) with no impingement over neurovascular bundle (orange arrowhead).

Table 1: Serial body impedance analysis, revealing persistence low skeletal muscle mass despite active in resistance exercise, and lower skeletal muscle mass at extremities

Date	16/11/2023	05/09/2024	05/12/24
Weight (kg)	48.4	49.5	49.2
Body mass index(kg/m2)	18.0	18.4	18.3
Skeletal muscle mass (kg)	16.3	17.9	17.3
Body fat mass (kg)	16.5	14.7	15.5
Percentage body fat (%)	34	29.7	31.5
Segmental Lean (kg)			
Right Upper limb	1.26	1.54	1.48
Right Lower limb	5.03	5.01	5.3
Left Upper limb	1.35	1.62	1.42
Left Lower limb	5.17	5.2	5.42
Trunk	14.3	15.6	15.0

retrograde ejaculation, which the patient had never associated with his neuromuscular complaints. This combination of progressive neurogenic weakness and unequivocal androgen insensitivity signs strongly pointed toward SBMA.

Nerve conduction study (Table 2) was done revealing bilateral upper limb sensory axonal neuropathy, right ulnar and bilateral fibular motor axonal neuropathy with bilateral median and ulnar midarm to forearm ratio reduced and abundant fasciculations on muscle ultrasound supporting the diagnosis of SBMA.

Genetic testing was initiated and identified a pathogenic CAG repeat expansion (48 repeats) in the AR gene, confirming the diagnosis of SBMA. Subsequent family history revealed an X-linked pattern of inheritance, with the patient's brother and several male cousins exhibiting similar symptoms, with some requiring wheelchair use in their fifth decade.

Table 2: The Nerve conduction study and electromyography of the patient

Sensory NCS	Bilateral median, ulnar and radial SNAP amplitudes were reduced with preserved conduction velocities. The sural SNAP amplitude and velocities were normal. Bilateral median to ulnar palm to wrist peak sensory latencies were not prolonged.
Motor NCS	Right ulnar and bilateral fibular nerves distal CMAP amplitudes were slightly reduced with normal distal motor latencies and conduction velocities. The split hand index were normal bilaterally.
F waves	Minimal F wave latencies were within normal limits.
Needle EMG	Needle EMG of the sampled muscles did not show any spontaneous activity nor any chronic denervation changes.
Nerve Ultrasound	Both right median and right ulnar midarm to forearm ratio were reduced.
Muscle Ultrasound	Muscle ultrasound demonstrated fasciculations over left biceps and left Flexor Digitorum, bilateral brachioradialis, bilateral vastus medialis and bilateral tibialis anterior.

CMAP: Compound Muscle Action Potential
EMG: Electromyography
NCS: Nerve Conduction Study
SNAP: sensory nerve action potential

DISCUSSION

The age of onset spans for SBMA from the second to seventh decade, typically manifesting in the fourth or fifth decade.[3] Initial symptoms frequently include tremor, muscle cramping, and focal weakness.[3] Neurological examination often reveals characteristic lower motor neuron signs: muscle atrophy, fasciculations involving the face and limbs, and hyporeflexia. Functional limitations often emerge as difficulty climbing stairs or walking extended distances. Weakness is typically both proximal and distal, may be asymmetrical, and is often more pronounced on the dominant side. Bulbar involvement is common, manifesting as dysarthria and dysphagia, with median onset in the early fifties, but not seen in this case.[4] Absence of bulbar signs does not exclude SBMA. Activity-dependent fatigue mimicking vascular claudication or tendinopathy is an under-recognized SBMA variant, reflecting selective vulnerability of large fast-twitch motor units and dorsal root ganglia involvement. Electrodiagnostic examination often reported diffuse denervation atrophy, anterior horn cell loss, and sensory neuronopathy. The diagnostic inflection point was recognition of long-standing gynecomastia and ejaculatory dysfunction features present for years but never elicited. This is the common androgenic insensitivity due to decrease in androgen receptor function.[3] Unlike amyotrophic lateral sclerosis or spinal muscular atrophy, SBMA uniquely combines lower motor neuron degeneration with partial androgen insensitivity.[3] This is the clue for suspecting SBMA.

This case yields two practical takeaways. First, serial body composition monitoring using accessible tools like BIA can provide objective evidence of a non-anabolic state that contradicts primary musculoskeletal pathology. When patients fail to build muscle despite documented adherence to resistance exercise and adequate nutrition, neurogenic atrophy must be excluded. Second, exertional weakness presenting as activity-induced fatigue or pain should not be reflexively attributed to deconditioning or peripheral vascular disease, particularly when associated with fasciculations or hyporeflexia.

In one clinical trial to test dutaseride efficacy for SBMA, the placebo group demonstrated an annual decline in muscle strength of 2% as measured by quantitative muscle assessment.[5] Interestingly, our patient's skeletal muscle mass remain static with no decline over the years. This highlight the important of resistance training in management of SBMA. Submaximal resistance training is well tolerated in spinal muscular atrophy and associated with modest strength gains; no study-related adverse events were reported.[6] One study even recommends high intensity training with improved fitness and workload in eight patients after eight weeks of training.[7] The majority of individuals with SBMA will have a normal lifespan and do not succumb to direct complications of the disease itself. Thus, it is important to advocate healthy lifestyle in this population.

Kennedy's disease remains underdiagnosed, with average delays exceeding five years. By recognizing anabolic failure as a quantifiable diagnostic clue and refocusing on the pathognomonic endocrine examination, clinicians can truncate the diagnostic odyssey and offer timely genetic counseling and supportive care. In addition, advocating exercise as part of management improves the quality of life of the patients.

DISCLOSURE

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