Case Report

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Kennedy's Disease and Progressive Muscular Atrophy: Diagnostic Overlap – A Case Report

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Abstract:

Kennedy's disease (KD), also known as spinal and bulbar muscular atrophy (SBMA), is a rare X-linked disorder of the lower motor neurons that may clinically resemble progressive muscular atrophy (PMA) variety of motor neuron disease, creating diagnostic challenges. We report a 50-year-old man with a 12-year history of progressive limb weakness, muscle wasting, and dysphagia. Examination revealed proximal muscle atrophy, tongue fasciculation, preserved reflexes, and testicular atrophy. Laboratory studies showed normal creatine phosphokinase with marginally elevated aldolase. Electromyography indicated chronic denervation, while imaging excluded central pathology. Genetic testing of the androgen receptor (AR) gene showed one allele within the normal CAG repeat range, leaving the presence of an expanded allele uncertain. This case lacks the characteristic clinical and EMG precision for PMA whereas the diagnosis of KD remains unsettled due to inconclusive DNA reports.

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Introduction:

Kennedy's disease (KD), also known as spinal and bulbar muscular atrophy (SBMA), is a rare X-linked lower motor neuron disorder with adult onset caused by an abnormal CAG repeat expansion in the androgen receptor (AR) gene. As with other X-linked recessive conditions, the disease manifests almost exclusively in males, while females typically remain carriers.[1]

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In KD, the CAG repeat is expanded to 37-60 copies, resulting in a defective AR protein that accumulates in motor neurons of the brainstem and spinal cord, as well as in muscle cells, leading to cellular toxicity and degeneration.[2]

Clinically, KD presents with slowly progressive limb weakness, muscle atrophy, bulbar involvement, and characteristic endocrine features such as infertility, insulin resistance, testicular atrophy, and gynecomastia. These endocrine manifestations reflect impaired androgen responsiveness due to the abnormal receptor.[3] The clinical picture may overlap with myopathies, progressive muscular atrophy (PMA), and other lower motor neuron disorders. PMA, a sporadic lower motor neuron disease, is a particularly important differential diagnosis, sharing features such as limb weakness and chronic denervation on electromyography.[4] Distinguishing between KD and PMA can be challenging, especially when genetic testing yields inconclusive results. This case report illustrates such a diagnostic dilemma and highlights the importance of integrating clinical, electrophysiological, and molecular data, as well

as the value of more sophisticated genetic testing methods.

Case summary:

A 50-year-old man presented with a 12-year history of slowly progressive weakness, muscle wasting, and dysphagia. The weakness initially affected the upper limbs, gradually progressed to the lower limbs, and was later accompanied by difficulty swallowing. His past medical history was notable for type 2 diabetes mellitus and cholelithiasis, diagnosed 6 years and 2 years earlier, respectively. He also reported chronic low back pain for the last year. He denied fever, cough, sputum production, joint pain (other than back pain), rash, trauma, or prior surgery. He was the father of two healthy sons and reported no similar illnesses among family members. On neurological examination, higher cerebral functions were normal and cranial nerves were intact. There were no sensory deficits or extrapyramidal features. Motor examination revealed marked wasting of all four limbs, most pronounced in the shoulder girdle muscles (Figure 1a, 1b). He was unable to raise his arms above shoulder level (Figure 1c) or to rise from a squatting position without assistance. No dysarthria was noted, but tongue fasciculation was present. Deep tendon reflexes were preserved and normal, and no upper motor neuron signs were elicited. Gynecomastia was absent, but the testes were soft and mildly atrophic. General physical examination, vital signs, and systemic evaluation of the chest, abdomen, and cardiovascular system were unremarkable. Routine blood tests, thyroid function (TSH), testosterone, creatinine, and electrolytes were normal. His diabetes was well controlled on oral gliclazide and metformin, with HbA1c measured at 5.5%. Serum creatine phosphokinase (CPK) was within normal limits, while antinuclear antibody (ANA) titers were weakly positive at 1:40, and serum aldolase was marginally elevated (Table 1). Neuroimaging revealed a normal MRI of the brain and cervical spine. MRI of the lumbosacral spine demonstrated a circum-ferential, central, and bilateral paracentral disc bulge at the L3–L4 level with thecal sac indentation, suggestive of a prolapsed lumbar intervertebral disc (PLID). Nerve conduction studies of all four limbs were normal; however, F-wave and H-reflex studies on electromyography (EMG) indicated features of chronic denervation. Testicular ultrasound revealed bilaterally reduced testicular volume. Upper gastrointestinal endoscopy was unremarkable, but a modified barium swallow demonstrated significant delay in swallowing with bolus retention, consistent with lingual and pharyngeal muscle dysfunction. Genetic analysis was performed using radioactive PCR to amplify the CAG repeats in exon 1 of the androgen receptor (AR) gene. The DNA study identified one allele within the normal CAG repeat size range, representing either a homozygous normal state or heterozygosity with a second expanded allele that failed to amplify by PCR.

Figure 1: Gross wasting of a) upper limb muscles b) shoulder girdle muscles and c) inability to raise hands above shoulders.

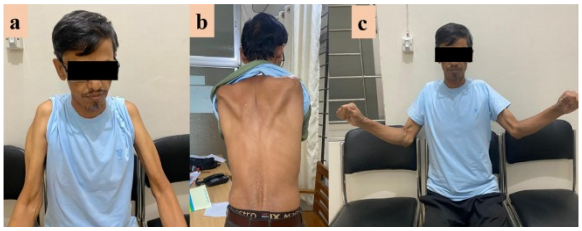

Table 1: Summary of blood test reports

	Name of test	***Report***
1	*CBC*	*Hb-12.5gm/dl, TC-5000/cu-mm, ESR- 06mm in 1st hour, DC-N66%, L31%, M02%, E01%, B00%,Platelet-2,20,000/cu-mm*
2	*CRP (mg/dl)*	*<0.5*
3	*RBS (mmol/L)*	*8.7*
4	*HbA1C (%)*	*5.5*
5	*Serum creatinine (mg/dl)*	*0.78*
6	*Serum electrolytes (mmol/L)*	*Na-141, K-4.2, Cl-110, HCO3-26*
7	*Serum TSH (µIU/mL)*	*0.99*
8	*Serum testosterone (nmol/L)*	*36*
9	*Serum ANA (titer)*	*1: 40*
10	*Serum aldolase (IU/L)*	*9.0*
11	*Serum CPK (IU/L)*	*85*
12	*Serum LDH (IU/L)*	*110*
13.	*Serum HBsAg*	*Negative*
14	*Serum Fasting Lipid Profile (mmol/L)*	*Total- 5.02, TG-1.5, LDL-2.8, HDL- 1.3*

Discussion

The global prevalence of KD is 1 to 2 in 100,000 people. Though estimation of the exact prevalence is difficult due to its clinical variability, gender bias, potential underdiagnosis, and the 'founder effect', it is universally considered as a rare condition.[5]

Considering the proximal upper limb muscle wasting and weakness, bulbar muscle denervation, slow progression, absence of upper motor neuron features, and the presence of endocrine manifestations such as diabetes mellitus and testicular atrophy, there is strong evidence supporting a diagnosis of spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease (KD).[6] However, establishing this diagnosis remains challenging for several reasons. Firstly, SBMA has a number of closely resembling differential diagnoses, including myopathies, muscular dystrophies, and other forms of motor neuron disease. Secondly, clinical features may vary, overlap, and fluctuate, making a straightforward diagnosis difficult. Moreover, test results- particularly genetic testing which may be inconclusive, adding further complexity to the diagnostic process.[7]

In the index case, the clinical presentation was inconsistent with primary muscle disorders such as myopathies and muscular dystrophies, which are typically caused by structural or metabolic defects within muscle fibers. In contrast, Kennedy's disease (KD) is a motor neuron disorder that results in secondary muscle atrophy.[8] Electromyography (EMG) revealed neurogenic changes, including large-amplitude, long-duration motor unit potentials, reduced recruitment, and chronic denervation- findings that clearly differ from a myopathic pattern.[9] The absence of upper motor neuron features effectively excluded amyotrophic lateral sclerosis (ALS). Although the case shared several features with progressive muscular atrophy (PMA), bulbar involvement, and normal creatine phosphokinase (CPK) levels made PMA an unlikely diagnosis. While bulbar involvement can theoretically occur in PMA, it is uncommon. Furthermore, endocrine manifestations such as diabetes and testicular atrophy are characteristic of Kennedy's disease, but are not seen in primary myopathies, ALS, or PMA.[4]

In the above clinical scenario, after clinically excluding the major differentials of KD, genetic testing could have provided a definitive diagnosis if the results were conclusive. Analysis of the androgen receptor (AR) gene in this case demonstrated one allele within the normal CAG repeat range; however, the presence of an expanded allele could not be confirmed. Such inconclusive results may occur because standard PCR-based techniques sometimes fail to amplify very large CAG expansions or may be limited in detecting both alleles, particularly in female carriers.[10] Testing of the patient's mother could have been informative, but she was not available for evaluation. In these situations, further analysis with more sensitive methods such as, triplet-primed PCR or Southern blot is recommended to clarify the genetic status.[11]

Conclusion

This case illustrates the diagnostic overlap between Kennedy's disease and progressive muscular atrophy, highlighting the challenges in distinguishing lower motor neuron disorders when clinical features are shared and genetic testing is inconclusive. Recognition of endocrine manifestations, careful electrophysiological assessment, and advanced molecular diagnostics are essential to establish an accurate diagnosis. Early identification of KD informs prognosis, family counseling, and monitoring for systemic complications. The case emphasizes the importance of heightened clinical awareness and the use of sensitive genetic testing methods in rare neuromuscular disorders with overlapping phenotypes.

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