A Case of Kennedy Disease and Literature Review

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Abstract: Kennedy disease, also known as spinal and bulbar muscular atrophy, is an X-linked neurodegenerative genetic disorder caused by mutations in the androgen receptor gene. The clinical manifestations typically initially present with slowly progressive proximal lower limb weakness, accompanied by androgen insensitivity symptoms such as tremor, muscle spasm, dysphagia, gynecomastia, and testicular atrophy. Herein, we report one case of Kennedy disease diagnosed at Hunan Provincial People's Hospital.

***Keywords*:** kennedy disease, spinal bulbar muscular atrophy, motor neuron disease, neurogenetics

1. Case Summary

A 63-year-old male patient was admitted to the hospital with the chief complaints of "gradually progressive unsteadiness in walking for 3 years and numbness and weakness in both lower limbs for half a year." Three years ago, the patient developed numbness in the right palm without obvious idiopathic, accompanied by generalized limb weakness, difficulty in rising from a squatting position, but no impairment of walking. The patient experienced muscle twitching in the lower legs, occurring 2-3 times a day, and finger flexion muscle spasm, occurring 2-3 times a week. These symptoms were induced by cold and relieved by stretching or massage. In the morning, the patient had no obvious numbness or weakness, but after 1 hour, mild swelling and numbness in both lower limbs developed, progressively worsening throughout the day. In the past six months, the patient noticed aggravation of limb numbness and weakness, leading to difficulty in walking, inability to stand for long periods, difficulty in ascending slopes, proneness to falls, and reduced strength in lifting heavy objects with both hands. Paresthesia in the left palm developed half a month ago.The patient was previously seen at a local hospital, where electromyography (EMG) revealed: Chronic neurogenic damage in the examined upper limb muscles and partial lower limb muscles, or possible chronic myogenic damage (myogenic damage in the chronic phase may show EMG changes similar to chronic neurogenic damage). EMG evidence of chronic myogenic damage in the medial head of the gastrocnemius muscles bilaterally. Polyneuropathy in all four limbs involving both motor and sensory nerves, with predominant sensory nerve involvement.The local hospital considered differential diagnoses of "etiology of bilateral lower limb weakness: myopathy? Mitochondrial brain disease?" and administered adenosylcobalamin for neurotrophic support. After treatment, numbness improved slightly, but weakness persisted. The patient denied headache, dizziness, dysphagia, dysphagia to liquids, chest band-like sensation, fever, or night sweats.

The patient had a history of cerebral infarction 7 years ago, with residual symptoms of slurred speech, right lower limb weakness, and deviation of the oral angle to the right. The patient also had a history of hypertension and diabetes mellitus. Since the age of 3, the patient occasionally experienced anterior tibial muscle pain, and sexual function ceased at the age of 40. There was no history of exposure to toxic substances or special medications.

2. Physical Examination

The patient was alert and oriented, with dysarthria but responsive. Physical examination revealed a shallow left nasolabial fold. Tongue protrusion was midline, with visible tongue muscle atrophy and fasciculation. The neck was supple without rigidity. Muscle strength: Right upper limb proximal strength was Grade 5 (normal), distal grip strength Grade 5−. left upper limb strength was Grade 5. Bilateral lower limb strength was Grade 5. Muscle tone in all extremities was normal. Deep tendon reflexes: Bilateral upper limb periosteal reflexes and lower limb knee reflexes were normal. Biceps reflexes and ankle reflexes were not elicited.Sensation: Cortical sensation and proprioception were intact. Hypalgesia was noted distally below the midpoint of both calves.

3. Auxiliary Examinations

Laboratory tests: Thyroid function panel (three items), thyroid-related antibodies (two items), anti-cyclic citrullinated peptide antibody, antiphospholipid antibody panel, rheumatology profile, immunology profile, lupus panel, cerebrospinal fluid (CSF) routine analysis, CSF biochemistry, CSF bacteriology, pre-transfusion screening, stool routine + occult blood

test, and urinalysis were all within normal limits. Myositis antibody panel was negative.Hormone levels: Estradiol 43.22 pg/mL, prolactin 13.82 ng/mL, testosterone 4.98 ng/mL.Serum enzymes: Lactate dehydrogenase (LDH) 354.1 U/L, creatine kinase (CK) 1922.9 U/L, creatine kinase-MB (CK-MB) 53.00 U/L, myoglobin 1411.60 ng/mL.

Electroneurography + Electromyography (EMG):

(1) Peripheral neuropathy.

(2) Needle EMG showed neurogenic and myogenic changes in the tested upper limb muscles. bilateral tibialis anterior muscles and the right sternocleidomastoid muscle revealed partial high-amplitude, long-duration motor unit potentials (MUPs).

Cranial MRI + MRA:

(1) Multiple punctate white matter hyperintensities in bilateral frontoparietal lobes and periventricular regions (presumed vascular origin, Fazekas grade 3).

(2) Encephalomalacic focus with hemosiderin deposition in the left basal ganglia.

(3) Intracranial atherosclerosis.

Genetic testing for Kennedy disease:

CAG repeat count in exon 1 of the AR gene was 40, consistent with the mutational profile of Kennedy disease (Figure 1).

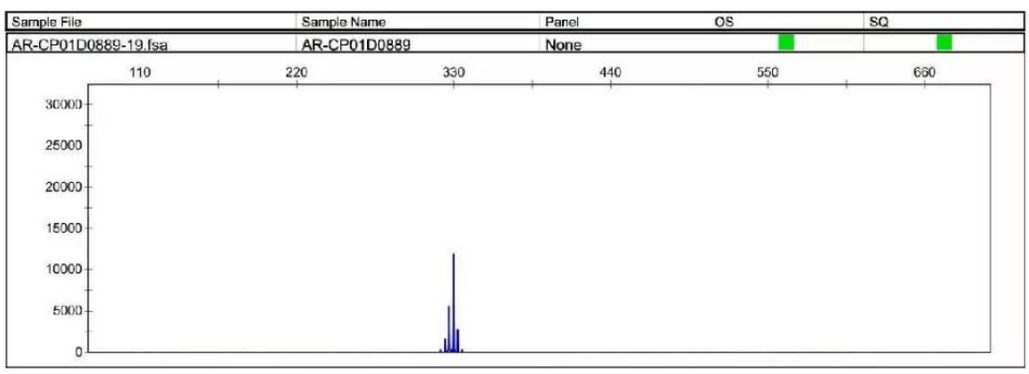

Figure 1. Genetic testing diagram

4. Discussion

The pathogenic gene of Kennedy disease is the androgen receptor gene, located at position Xq11-q12 of the X chromosome. Genetic testing is the gold standard for diagnosing this disease, but many patients are missed diagnosis due to economic reasons that preclude them from completing the examination. Literature reports indicate that the average CAG repeat sequence in Kennedy disease patients is 46, with a minimum of 40. Onset typically occurs between 30-50 years of age, predominantly affecting males[1]. Symptoms in homozygous females are also mild, often manifesting only as subtle muscle spasm and other non-specific signs. The age of onset correlates with the number of CAG repeats: the higher the repeat count, the earlier the disease onset[2, 3]. In late-stage disease, serum creatine kinase levels increase, which may be positively correlated with disease severity[4].

This patient presented with progressively worsening bilateral lower limb weakness as the initial symptom, which differs from the painful muscle spasm described as the first manifestation in Kennedy's original report[5]. However, most patients with Kennedy disease still seek medical attention due to muscle weakness, typically manifesting as progressive proximal lower limb weakness accompanied by muscle atrophy. Neurological symptoms may also include tongue muscle atrophy, fibrillation, and characteristic asymmetric facial muscle weakness. In advanced stages, dysphagia and sensory system abnormalities may occur. Non-neurological symptoms can include reduced male reproductive capacity, gynecomastia, and other androgen insensitivity manifestations. The patient in this case had a history of sexual dysfunction before the diagnosis of Kennedy disease was established.

Kennedy disease shares clinical similarities with many neuromuscular disorders, requiring careful differentiation from limb weakness caused by: Amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA), adult spinal muscular atrophy (SMA). Immune-mediated diseases such as myasthenia gravis and polymyositis. Other genetic disorders like muscular dystrophy and mitochondrial diseases.

Statistically, the average time from the first onset of muscle weakness to definitive diagnosis is 5.5 years or longer[6].

For example, patients with lumbar spondylopathy may also present with lower limb weakness, but MRI can effectively visualize most spinal lesions. In contrast, lumbar MRI in KD shows no spinal abnormalities, while limb imaging reveals muscle atrophy. Myasthenia gravis is characterized by diurnal fluctuation (symptoms worse in the evening, better in the morning), exertion-induced weakness or exacerbation, preserved tendon reflexes, positive repetitive nerve stimulation test, thymic hyperplasia on CT, and responsiveness to cholinesterase inhibitors [7]. In contrast, Kennedy disease does not exhibit diurnal variation in weakness, shows reduced or absent tendon reflexes, nonspecific repetitive nerve stimulation results, normal thymus, and no response to cholinesterase inhibitors.

Although the pathogenic gene of Kennedy disease has been identified for years, effective treatments remain limited. The mechanisms underlying motor neuron damage and muscle atrophy are complex, with proposed hypotheses involving nuclear inclusions, DNA damage, mitochondrial dysfunction, and other factors related to neuronal apoptosis[8]. Current clinical trials focus on agents such as: Gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide) [9-11]. Luteinizing hormone-releasing hormone (LHRH) analogs (e.g., goserelin)[12]. 5α-reductase inhibitors (e.g., dutasteride)[13]. Creatine monohydrate [14]. Mexiletine hydrochloride [15].These therapies target diverse pathways, including reducing testosterone production/release, lowering dihydrotestosterone levels, improving motor function via creatine supplementation, and alleviating cold-induced weakness or myotonic-like contractions. However, robust clinical data are still needed to validate their efficacy and safety.

In conclusion, genetic testing remains the gold standard for diagnosing Kennedy disease. Continued exploration of its pathogenesis and development of effective treatments are warranted. Early detection, diagnosis, and intervention may help delay disease progression[8].

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