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Case Report

Using genetic testing to diagnose Kennedy's disease: a case report and literature review

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Abstract: Theoretical basis: Kennedy's disease (KD) is also known as spinal bulbar muscular dystrophy. Because the symptoms of KD are similar to most neuromuscular diseases, it is difficult to make a rapid clinical diagnosis. Patient case: We report the case of a 50-year-old man who was diagnosed with "lumbar disc herniation" five years ago because of progressive proximal limb weakness. After his initial diagnosis, his condition worsened gradually, and a muscle biopsy was performed 3 years ago, and he was then diagnosed with "motor neuron disease", but he had no such family history. His physical examination showed female breast development, erectile dysfunction, a weakness of the quadriceps femoris, a bilateral tendon reflex, and atrophy of the tongue muscle. One year ago, it was found that his blood sugar had increased, and when oral hypoglycemic drugs were given, his blood glucose control was not ideal. At the same time, it was found that his creatine kinase continued to increase significantly. He was admitted to the hospital again because of the aggravation of his walking difficulties. Diagnosis: A laboratory examination showed elevated creatine kinase, an impaired glucose tolerance, and abnormal lactate values. The diagnosis was confirmed using a genetic analysis, which showed a repeated amplification of CAG in the androgen receptor gene. Intervention measures and results: After this diagnosis, the patient had a good prognosis after receiving symptomatic treatment. Lesson: Genetic testing is the key to the diagnosis of KD. Clinicians should make a differential diagnosis, an early diagnosis, and provide treatment as soon as possible according to the patient's clinical manifestations and laboratory examination.

Keywords: Case report, genetic analysis, Kennedy's disease

Introduction

Kennedy's disease (KD) is a motor neuron disease with a -+4X- linked recessive inheritance. The disease was first reported by Kennedy in 1968 [1]. In 1991, La Spada et al. mapped its pathogenic gene to Xqll-12. The disease is caused by an increase in the number of CAG repeats in exon 1 of the androgen receptor (androgen receptor, AR) gene [2]. Therefore, determining the number of CAG repeats in the AR gene is the gold standard for its diagnosis.

Kennedy's disease usually begins in middle age and has a chronic course of disease. The main clinical manifestations are weakness and atrophy of the muscles of the bulb and the extremities. More than half of the patients develop a weakness in both lower limbs, accompanied by a weakness in the bilateral muscles and masseter muscles, a decreased movement of the uvula and soft palate, and atrophy and fibrillation of the tongue muscles [3]. A few cases may be accompanied by autonomic nervous dysfunction, cognitive dysfunction, and other symptoms [4]. In addition, most patients also develop incomplete androgen insensitivity syndrome, with symptoms such as infertility and the production of male breast milk [5]. Endocrine tests show that most patients have elevated levels of serum creatine kinase [6], and some patients also suffer from hyperlipidemia, abnormal liver function, and poor glucose tolerance [7].

The number of CAG repeats in exon 1 of the AR gene in normal subjects is about 13-30 times, but in patients with Kennedy's disease the exon is 2.3 times its normal length [8]. The latest (EFNS) guidelines of the European Union of

Neuroscience take the number of trinucleotide CAG repeats in the first exon of AR gene ≥ 35 as the basis for the diagnosis [9].

A recent case of KD diagnosed using genetic testing in the department of neurology of our hospital is reported as follows.

Case report

The patient, a 50-year-old male, was admitted to our hospital 5 years ago because of left lower limb weakness. Lumbar magnetic resonance imaging was performed, and the result was considered to be "lumbar disc herniation". Oral vitamin B1 and mecobalamin were given for the treatment, but the symptoms did not improve. Half a year later, the patient's right lower limb began to show symptoms of weakness, such as an increased sense of powerlessness when walking for a long time, aggravation when going uphill and up the stairs, but without limb numbness or pain. He had been treated in a local hospital and was given surgical treatment for "lumbar disc herniation". The postoperative effect was not good. After that, the condition worsened gradually. A muscle biopsy was performed 3 years ago, and he was diagnosed with "motor neuron disease", but he did not receive any special treatment.

Two years ago, the patient gradually developed symptoms such as weakness of both upper limbs, a trembling voice, unclear speech, and atrophy of the tongue muscles, as well as a sense of his muscles in the extremities beating. One year ago, it was found that his blood sugar increased, so oral hypoglycemic drugs were given, but his blood glucose control was not ideal. At the same time, it was found that his creatine kinase level continued to increase significantly. In the past 3 months, the patient was admitted to the hospital again because of squatting difficulty, weakness of the limbs, and difficulty walking, and he was admitted with limb weakness to be examined in the hospital by its outpatient department.

Family history: the patient's one daughter, two parents, two sisters, and one nephew had no similar symptoms.

Ethics committee approval statement: The study was approved by the internal review board of the institutional ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient.

Physical examination: a clear consciousness, normal development, good nutrition, male breast development, no abnormal external genitalia. Vague speech, tongue muscle atrophy, tremors. The proximal muscles of both lower limbs were slightly atrophied, and he had difficulty squatting. His facial muscles beat while he was talking, but there was no clear atrophy of the bilateral scapular muscles, hand interosseous muscles, thenar muscles, fibula muscles, or the tibialis anterior muscles. His muscle strength in both the upper limbs was 5-grade, his proximal muscle strength in both the lower limbs was 5-grade, and his distal muscle strength was 4 grade. His deep and shallow sensations were normal, his double upper limb tendon reflexes were symmetrically weakened, and his double lower limb tendon reflex were not drawn out pathologically (1).

Laboratory examination: liver function: alanine aminotransferase 55.7 U/L (reference value: 0~40 U/L) and aspartate aminotransferase 40 U/L (reference value: 0~37 U/L). Fasting blood glucose 10.02 mmol/L (reference interval 3.9-6.1 mmol/L) and glycosylated hemoglobin 7.3% (4%-6%). Blood lipids: triglyceride 10.69 mmol/L (reference value: < 1.7 mmol/L), total cholesterol was 8.04 mmol/L (reference value: < 5.15 mmol/L). Sex hormones: testosterone 719.5 ng/dl (reference value: 358-1217 ng/dl), estradiol 56.9 pg/ml (reference value: 19.9-47.9 pg/ml), pituitary prolactin 17.8 ng/ml (reference value: 2.1-11.7 ng/ml). Creatine kinase 660 U/L (reference interval 24-190 U/L), creatine kinase isoenzyme 26.9 U/L (reference interval 0-25 U/L), triglyceride 8.74 mmol/L (reference interval 0.4-1.86 mmol/L). No significant abnormalities were found in the patient's blood routine, routine defecation, renal function, electrolytes, rheumatoid factor, ESR, thyroid function, tumor, connective tissue, vasculitis, or cerebrospinal fluid examinations. ECG: sinus rhythm, roughly normal ECG. MRI of the head and cervical vertebrae showed that no obvious abnormality was found on the plain scan of the head. Intervertebral disc herniation was found in C3/4 and C4/5. Lumbar CT

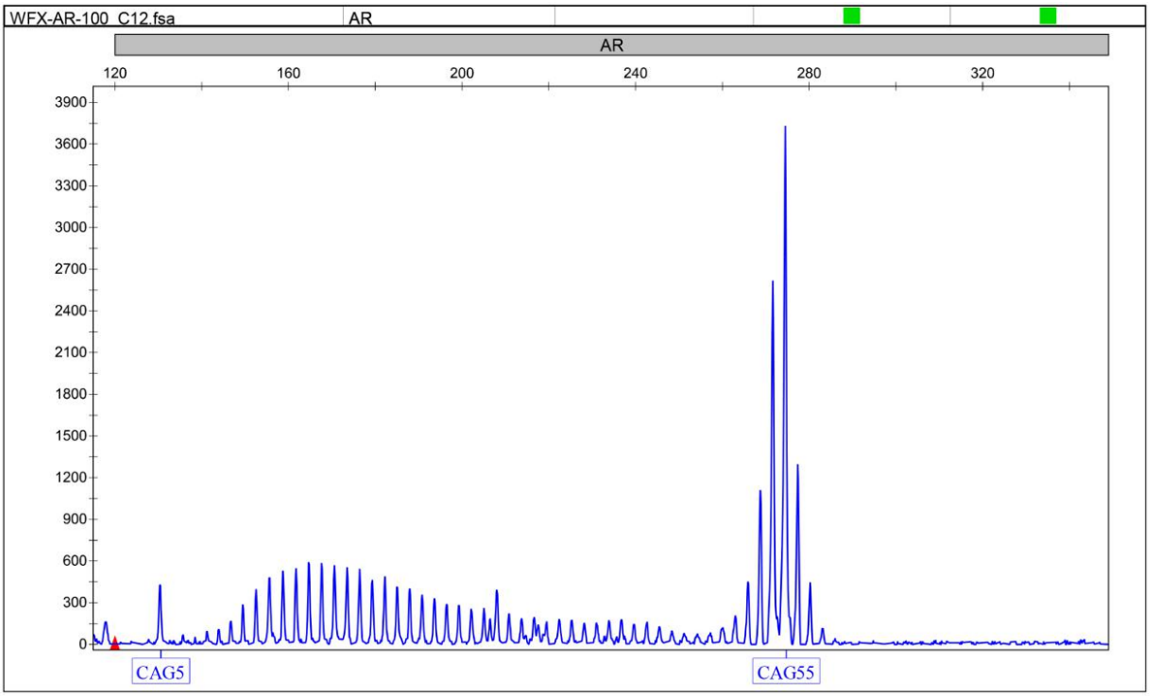

Figure 1. The results of the capillary electrophoresis showed that the number of the CAG repeats in exon 1 of AR gene was 55.

showed lumbar disc herniation in L3/4 and L4/5. Electromyography: the conduction velocity of the sensory branch of the right median nerve and the right ulnar nerve were slowed down, the conduction velocity of the motor branch of the bilateral common peroneal nerve was slowed down, the latency of the endings were prolonged, and the amplitude of the sensory branch of the bilateral superficial peroneal nerve was decreased. The conduction velocity of the sensory branch of the right superficial peroneal nerve was slowed down, and the conduction velocities of the other examined nerves were not abnormal. There was no obvious abnormality in the F wave of the bilateral median nerve or the H reflex of the bilateral tibial nerve.

The genetic testing showed that "the number of CAG repeats in exon 1 of AR gene was 55, which is consistent with the genetic characteristics of Kennedy's disease" (**Figure 1**). After the symptomatic treatment, the prognosis is good.

Treatment: The patient did not receive any anti-androgen therapy, gene therapy, or muscle directed therapy because of personal reasons. He received one week of neurotrophic drugs and anti-symptomatic treatment, but the symptoms did not improve significantly.

Discussion

In 1991, La Spada et al. studied 35 unrelated patients with Kennedy's disease and found that the copy number of trinucleotide repeat CAG in exon 1 of the androgen receptor AR gene was abnormally amplified in the patients, with the repeat number reaching 40.52 times, but no dynamic mutations were found in the 75 healthy controls. It was confirmed that the disease was caused by an increase in the number of repeats in the CAG sequence in the AR gene [2]. Studies have shown that the number of CAG repeats has nothing to do with the progression rate of Kennedy's disease, but it is related to the patient's age at the onset of the disease, that is, the higher the number of CAG repeats, the earlier the age of onset. In addition, the latest study on the relationship between nerve conduction and the number of CAG repeats shows that the higher the number of CAG repeats, the more significant the patient's motor nerve symptoms are, but if the number is lower, the sensory nerve symptoms are significant [10]. As a result, some scholars have proposed classifying a CAG repetition number ≥ 47 as the

motor dominant type and a CAG repetition number < 47 as the sensory dominant type. Patients with the sensory dominant type often also suffer from postural tremors of the thigh [11].

In other diseases with abnormal AR receptors due to genetic mutations, the patients exhibit androgen insensitivity, but there is no progressive limb weakness. Therefore, some scholars speculate that the mutated AR protein causes disease through the following two mechanisms: (1) the loss of normal AR receptor function makes patients show an androgen insensitivity. At the same time, the motor neurons lacking the normal AR protein will undergo degeneration and necrosis. (2) abnormal AR proteins will have toxic effects on the motor neurons [8]. It has been confirmed that the toxicity of the mutant AR protein is ligand-dependent, in other words, Kennedy's disease is an androgen-dependent disease. In transgenic fruit fly experiments, because fruit flies do not have endogenous androgens, mutated genes have no effect on fruit flies unless they are given food containing androgens [12]. In transgenic mice, even if the mutated gene is not on the X chromosome, only male mice develop the disease. The symptoms of castrated male rats improved, but the female rats treated with exogenous androgens gradually developed the symptoms of Kennedy's Disease [13]. In the clinical case observation, it is found that even if the female has a homozygous mutation, there will be no or only mild clinical symptoms [14]. The above evidence shows that Kennedy's disease is only affected by males, not only because it is an X-linked recessive genetic disease, but also because it is an androgen-dependent disease.

In the past 10 years, there has been a breakthrough in the study of the pathological mechanism of Kennedy's disease. At present, it is considered that related gene transcriptional disorders, mitochondrial dysfunction, oxidative stress responses, and neuronal axonal transport disorders are also the key links in the pathogenesis of Kennedy's disease [15]. The latest research shows that endoplasmic reticulum stress not only plays an important role in the pathogenesis of Kennedy's disease, but it also provides a new target for the treatment of Kennedy's disease [16]. The endoplasmic reticulum, which exists in the cytoplasm, is an important organelle for protein synthesis and modification in cells. When a large number of proteins are misfolded and Ca^{2+} homeostasis disorders exist in cells, they will cause endoplasmic reticulum stress, which leads to a persistent disorder of the endoplasmic reticulum function and initiates cell death pathways, leading to cell degeneration and death [16].

This disease needs to be distinguished from the following diseases: (1) Amyotrophic lateral sclerosis: the disease progresses rapidly, with double upper limb muscle atrophy and myodynamia in the early stage, the distal end is more severe than the proximal end, and the upper and lower motoneurons are involved. It can occur in both men and women, and there is no breast development. (2) Spinal muscular dystrophy (spinal muscular atrophy, SMA): This is a group of hereditary diseases, most of which have a recessive inheritance, which is related to the stock gene of the motor neurons on autosomal chromosome 5. The main clinical manifestation is progressive symmetrical proximal myasthenia atrophy. The patients are divided into four types, in which the onset age of types I-III was infants, children, and adolescents, while the onset age of type IV was 18-60 years old. This can affect females, but there is no male breast development or other endocrine changes and sensory symptoms. The clinical manifestations, age of onset, and clinical electrophysiology are difficult to distinguish from KD, so genetic testing is an important means of differentiation; (3) Becker muscular dystrophy (Becker muscular dystrophy, BMD): 5-15 years old, first involves the pelvic band muscle and lower limb proximal muscles, gradually spreads to the scapular machine, and there is gastrocnemius or deltoid muscle pseudo-hypertrophy. The serum creatine kinase level increases significantly, more than ten times or even tens of times more than normal. The EMG and muscle biopsy show myogenic damage, and the muscle nuclear magnetic resonance shows that the degenerative muscle has an "insect erosion". (4) Polymyositis: acute or subacute onset, the age of onset is not limited, affects females more than males, and there tends to be a history of low fever or colds before onset, and it is characterized by a weakness of the proximal extremities accompanied by dysarthria and joint muscle pain. Most patients have an increased erythrocyte sedimentation rate, increased C-reactive protein, and so on. The increase in the serum creatine kinase level is often

ten times or even dozens of times higher than the normal level, and the urinary creatine is increased. The muscle biopsy shows a large amount of muscle fiber necrosis, regeneration, and inflammatory cell infiltration, and the expression of CD8 can be seen in the muscle nucleus, and a positive MHC-1 stain can be found on the muscle cell membrane. Spontaneous fibrillation potential and positive sharp wave are observed in the electromyography.

At present, there is no specific treatment for the disease, just symptomatic treatment. It has been reported that leuprorelin may have a certain effect on delaying the progression of the disease if the course of the disease is less than 10 years [17]. Existing methods can prevent the heredity of the disease in the family through "amniocentesis", "prenatal diagnosis", and "the artificial induction of labor". Single cell gene analysis can also be used to select fertilized eggs without the pathogenic genes for in vitro fertilization, which can ensure that the embryos do not carry the pathogenic genes and achieve the eugenic goal for the female KD gene carriers.

In conclusion, Kennedy's disease is rare, and its clinical manifestations are heterogeneous, so it is easy to miss the diagnosis. Genetic testing is the key to the diagnosis of KD. Clinicians should make a differential diagnosis, an early diagnosis, and should provide early treatment as soon as possible according to the patients' clinical manifestations and laboratory examinations.

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Disclosure of conflict of interest

None.

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