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Case study

Endocrinal description of two Chinese Kennedy's disease pedigrees

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ABSTRACT

Kennedy's disease (KD), also known as X-linked spinal and bulbar muscular atrophy (SBMA), is caused by the expansion of cytosine-adenine-guanine (CAG) repeats in the first exon of the androgen receptor (AR) gene. KD is a late-onset neural-endocrinal disease that is characterized by the degeneration of motor neurons in the brainstem and spinal cord. In addition, partial androgen insensitivity is an important manifestation of KD. Here, we report two Chinese KD pedigrees that reveal the clinical and genetic manifestations and fully elaborate the endocrinal characteristics of KD patients. The proband in pedigree 1 was referred to an endocrinologist for gynaecomastia and sexual dysfunction. A gene analysis of this patient revealed that there were 53 CAG repeats in the AR gene. A family survey identified an additional two KD patients in pedigree 1. The proband in pedigree 2 was diagnosed by a neurologist and did not have gynaecomastia or sexual dysfunction. A family survey identified an additional subclinical patient, and both patients exhibited partial androgen insensitivity at a hormonal level. We therefore suggest that a family survey and hormone tests should be routinely performed in KD patients and that physicians should increase their understanding of the different symptoms of KD to achieve correct diagnoses in affected patients.

1. Introduction

The androgen receptor (AR) gene is located in Xq11-12 and contains a cytosine-adenine-guanine (CAG) repeat sequence that encodes a polyglutamine tract in its first exon. A marked expansion in the length of these CAG repeats (CAG repeats >38) results in Kennedy's disease (KD), which is also called X-linked spinal and bulbar muscular atrophy (SBMA) [1]. KD is an adult-onset, slowly progressive motor neuron disease that only fully manifests in males. Female carriers and female homozygotes show only slight symptoms [2]. KD patients mainly manifest with bulbar and proximal limb muscle weakness, muscle atrophy and tremor. In addition, affected males often exhibit the clinical features of mild androgen insensitivity, which include gynaecomastia, reduced fertility and testicular atrophy in adulthood [3]. However, in KD, the symptoms associated with androgen resistance are considered secondary to its neurological symptoms and have therefore not been paid as much attention. Nearly all KD patients are diagnosed by neurologists, and few KD patients are diagnosed by endocrinologists [4,5]. Here, we report two Chinese KD pedigrees and fully describe the endocrinal manifestations of KD in the affected individuals in these families.

2. Case report

2.1. Pedigree 1

The proband of pedigree 1 is a 33-year-old male who visits an endocrinologist to treat gynaecomastia and sexual dysfunction. He developed gynaecomastia at the age of 19 and underwent a surgery to treat it at the age of 23, but the gynaecomastia later relapsed. He was diagnosed with asthenospermia at the age of 27 but had a baby girl at the age of 28. Three years ago, the patient was referred to our centre because of his gynaecomastia. At that time, he was found to have elevated levels of testosterone and luteinizing hormone (LH). The diagnosis was gynaecomastia (partially androgen-resistant) and pituitary non-functional microadenoma, and follow-up was advised. In the most recent year, he had complained about sexual dysfunction, and his wife had difficulty conceiving after they had planned to have another child in the most recent half-year. The patient was therefore referred to our centre for further evaluation.

On questioning, the proband reported trembling in the hands from the age of 17. His mother's two brothers reported muscle

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weakness and muscular atrophy, and one of them was infertile. On physical examination, the proband exhibited bilateral breast development, a typical pubic hair distribution and normal external genital organs. A neurological examination revealed tongue fasciculations, tongue atrophy and hand tremor. Dysphagia and dysphonia were absent. A motor examination showed that the proband had a well-developed musculature without atrophy, weakness or fasciculation. He had a normal gait and was able to arise from a squatting position unassisted.

The patient's serum levels of creatine kinase (CK), LH, oestradiol, testosterone and sex hormone-binding globulin (SHBG) were elevated (CK: 227 U/L, normal 34–174 U/L; LH: 10.3 mIU/ml, normal 1.7–8.6 mIU/ml; oestradiol: 238.1 pmol/L, normal 28–156 pmol/L; testosterone: 32.5 nmol/L, normal 9.9–27.8 nmol/L; and SHBG: 65.5 nmol/L, normal 18.3–54.1 nmol/L). His levels of thyroid-stimulating hormone, free thyroxin, fasting plasma glucose (FPG), postprandial plasma glucose, dehydroepiandrosterone sulfate (DHEAS), progesterone and prolactin were normal. Total cholesterol serum levels were within the normal range. His serum level of triglyceride was elevated (2.64 mmol/L, normal 0.60–1.70 mmol/L), and his serum level of high-density lipoprotein-cholesterol was low (0.85 mmol/L, normal >1.04 mmol/L). A gonadotropin-releasing hormone (GnRH) test resulted in a relatively high LH response (7.4 mIU/mL to 42.0 mIU/mL). A semen analysis showed that his sperm concentration was normal, while sperm movement was low (progression 3.19%). Electromyography (EMG) showed evidence of widespread denervation in his muscles and axonal degeneration in sensory nerves. KD should be considered in patients with androgen insensitivity and typical EMG results. We therefore conducted a family survey and gene analysis of the family (Fig. 1). The results showed that the number of CAG repeats in the proband was 53 (Fig. 2) and that his two uncles had the same number of CAG repeats. There were therefore three KD patients in the family. In addition, the proband's mother and daughter were gene carriers with 53/25 and 55/25 CAG repeats, respectively, even though neither of them showed any symptoms.

2.2. Pedigree 2

The proband of pedigree 2 was a 54-year-old male. He was referred for muscle weakness and muscle atrophy. He reported that lower limb weakness began 3 years ago and that these symptoms had progressed slowly. In the most recent year, weakness had appeared in his upper limbs. Muscular atrophy, choking and dysphasia had appeared in the most recent two months. He had had Type 2 Diabetes Mellitus and hypertension for ten years and was being treated with gliclazide, valsartan and amlodipine. He had a son at the age of 24. On questioning, the patient did not report any complains related to sexual dysfunction. His mother's father, who had passed away, had susceptible neuromuscular disorder. In addition, no other member of the family had reported related clinical manifestations.

A neurological examination showed absent tendon reflexes and reduced vibration. A motor examination revealed proximal limb muscle atrophy and weakness, and muscle fasciculation was observed in the neck and the right thigh. He has a normal gait but had difficulty rising from a squatting position. Tongue atrophy, tongue fasciculations, dysphasia, dysphagia and an absent pharynx reflex were documented. On physical examination, no gynaecomastia or testicular atrophy was observed.

The levels of FPG, haemoglobin A1c, CK, LH, oestradiol, testosterone and carcinoembryonic antigen (CEA) were elevated (FPG: 14.0 mmol/L, normal 3.9–5.6 mmol/L; haemoglobin A1c: 10.3%, normal 4.0–6.0%; CK: 380 U/L, normal 34–174 U/L; LH: 9.9 mIU/ml, normal 1.7–8.6 mIU/ml; oestradiol: 169.4 pmol/L, normal 28–156 pmol/L; testosterone: 32.2 nmol/L, normal 9.9–27.8 nmol/L; and CEA: 6.2 ng/mL, normal <5 ng/mL). The results of tests for liver function, renal function, autoimmune antibodies, hepatitis A, B, C, D, and E viral antibodies, folic acid, vitamin B12, serum copper, and ceruloplasmin were all within the normal range. The levels of progesterone, DHEAS, SHBG and prolactin were normal. Electromyography showed evidence of widespread denervation of the muscles in the limbs, rectus abdominis muscle and the muscles supplied by the accessory nerve. Additionally, axonal degeneration was observed in the sensory nerve. Brain MRI revealed a lacunar infarction. No evidence of a tumour was found.

We conducted a survey of the family, and gene sequence analyses were performed on 15 family members (Fig. 3). The results showed that the proband had 49 CAG repeats in the first exon of the AR gene and that another subclinical patient in the family had the same number of CAG repeats. The subclinical individual was a 34-year-old male whose main presentations were subclinical fasciculation in the hands, while gynaecomastia and sexual dysfunction were absent. Testosterone and DHAES levels were ele-

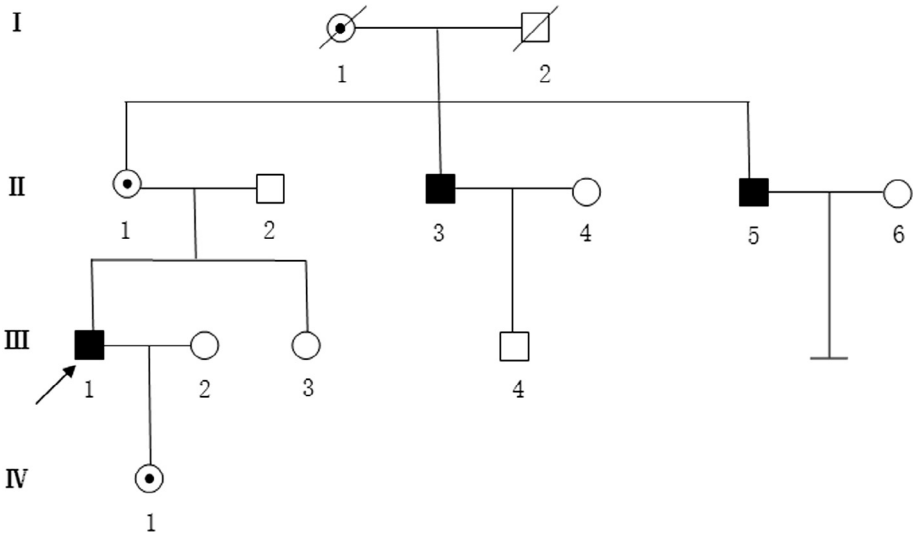

Fig. 1. Family tree of pedigree 1. ■male patient □health male ⊙female gene carrier ○health female /departed ↗proband. There are 3 Kennedy's disease patients (III 1, II3, II 5), 2 female gene carriers (II 1, IV 1) and 6 health persons (II 2, II 4, II 6, III 2, III 3, III 4) in the family.

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