Kennedy Disease Mimics Amyotrophic Lateral Sclerosis: A Case Report

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Abstract- Kennedy disease (KD) is an X-linked inherited motor neuron disease that is often accompanied by androgen insensitivity. Its estimated incidence in the US is approximately 1 case in 40,000 men. KD has also been reported in individuals of different racial backgrounds, especially in Japanese but the prevalence rate in Taiwan has not been fully investigated. Here we report a case of KD definitely diagnosed by abnormal expansion of a polymorphic tandem cytosine-adenine-guanine (CAG) triplet repeat in the first exon of the androgen receptor gene. The direct genotyping from polymerase chain reaction product is subsequently performed utilizing capillary electrophoresis. The patient's neurological conditions mimic amyotrophic lateral sclerosis (ALS). Since these two diseases have different etiologies and prognosis, it reminds us the necessity to rule out KD in face with a suspected male case of ALS.

Key Words: Kennedy disease, CAG triplet repeat, Androgen receptor gene, Polymerase chain reaction, Capillary electrophoresis, Amyotrophic lateral sclerosis (ALS)

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INTRODUCTION

Since the first report in 1968 on a slowly progressive form of an X-linked spinal and bulbar muscular atrophy and the discovery of its molecular background in 1991, Kennedy disease (KD) has increasingly drawn attention[1]. The typical clinical presentations of KD are slowly progressive proximal limb and bulbar weakness, decreased tendon reflex, muscular atrophy, ubiquitous fasciculations with predominance on facial muscles, postural tremor and non-neurologic symptoms such as gynecomastia. In addition, elevated serum creatine kinase (CK) and alanine aminotransferase (ALT) levels, lipid disorders and endocrinopathy including glucose intolerance, and androgen insensitivity are found in many patients[2,3]. Several case studies have been reported in Taiwan[4-6], including a case report with clinical presentation of sensory neuropathy[4].

KD is caused by an expansion of a polymorphic tandem cytosine-adenine-guanine (CAG) triplet repeat in the first exon of the androgen receptor gene encoding a polyglutamine stretch[1,7]. Because its clinical symptoms

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overlap with some other neuromuscular disorders, for example, amyotrophic lateral sclerosis (ALS) or spinal muscular atrophies, KD sometimes is misdiagnosed or left unnoticed[8]. Here we present a case of KD confirmed by the genetic testing who showed slowly progressive proximal limb weakness, generalized fasciculation but hyperreflexia that mimics ALS.

CASE REPORT

This 37-year-old man worked as a computer-programming engineer denied any systemic disease or taking regular medication in the past. He noted intermittent twitching over face and bilateral arms in recent 3 years and an insidious onset of leg weakness exacerbated in recent one year causing difficulty in climbing stairs. Once in a while, he also felt numbness over posterior aspects of both thighs and nasal tone developed after prolonged speaking. These symptoms did not occur at particular timing or show a diurnal change. Even though these symptoms developed insidiously but seemed exacerbated progressively, so he came to our hospital for check up. On admission, physical examinations showed a normal weighted man with baldness, gynecomastia, tongue atrophy (Fig. 1A and 1B) and mild muscle wasting over the proximal portion of four limbs. There was no testicular atrophy and sexual characteristics were normal. Baldness and enlarged breasts developed since adolescence. A neurologic examination disclosed mild proximal weakness of four extremities, which was around grade 5- in Medical Research Council (MRC) of Great Britam scale. Diffuse fasciculation over bulbar and limbs musculature and generalized brisk tendon reflexes (all tendon reflexes were +++ except grade ++ noted in bilateral ankle jerks) were also found. There was no limb spasticity, Hoffman sign nor clonus. There was no definite sensory deficit and plantar reflex remained flexed. In family history, his relatives have no similar symptoms, including his elder brother and his daughter.

Because diffuse lower motor neuron involvement with generalized hyperreflexia, ALS was impressed; however the coexisted gynecomastia points to the possibility of KD. In the blood tests, the complete blood count, hormone and immune profiles including thyroid function, androgen and estrogen levels, erythrocyte sedimentation rate and C-reactive protein were within normal limits; rapid plasma reagin screening test, rheumatoid factor and antinuclear antibody test were negative. Serum luteinising hormone level was 3.88 IU/L, follicle-stimulating hormone concentration was 1.57 IU/L, and prolactin level was 11.6 ng/mL. The plasma estradiol level was 28.1 pg/mL and his testosterone concentration was 4.73 ng/mL. Biochemical study revealed sugar 149mg/dL, CK up to 1762 U/L, asparate aminotransferase 50 U/L, ALT 59 U/L and hypertriglycemia (218mg/dL). Brain magnetic resonance imaging did not show any abnormality. Spine X-rays revealed mild cervical spondylosis, scoliosis of lumbar spine and retrolisthesis from L3 to S1. Nerve conduction studies showed normal sensory nerve action potentials and compound muscle action potentials with normal conduction velocities and distal latencies. F-wave studies of bilateral median, ulnar, peroneal, and tibial nerves revealed nor-

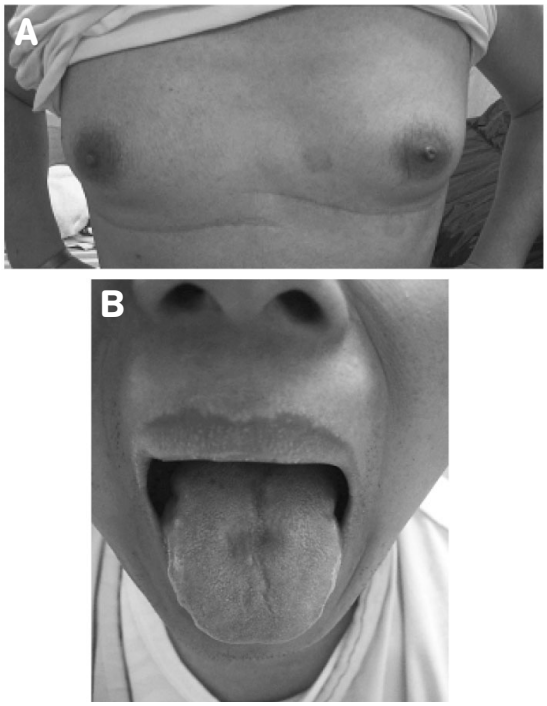

Figure 1. The characteristic clinical features of Kennedy's disease. (A) Gynecomastia and (B) tongue atrophy with increased wrinkling and deep central furrow.

mal results. Needle electromyography showed fibrillations, fasciculations and reduced recruitment with large, fast-firing motor units in many tested muscles especially in the deltold, biceps, triceps, pectoralis, quadriceps, and periocular muscles (Fig. 2).

DNA was extracted from peripheral blood leukocytes. Exon 1 of androgen receptor gene was amplified by polymerase chain reaction (PCR) according to the proposed protocol[9,10]. Size of the PCR product was determined by the capillary electrophoresis (CE) method[9] with the HDA-GT12TM System (eGene, Inc. Irvine, CA, USA). The size of the PCR product revealed 387 base pairs, which corresponds to 67 CAG triplet repeats in the androgen receptor gene on the X chromosome that coincides with the genetic defect of KD (Fig. 3). Genetic counseling was also arranged for his elder brother and CAG triplet repeats was 23, within in the normal range (17 to 26 repeats) in normal healthy individuals.

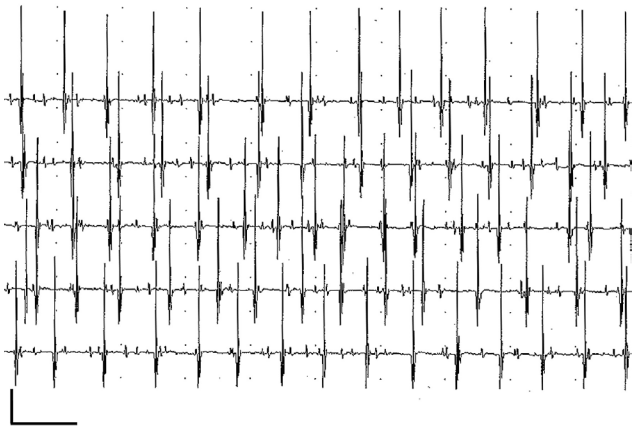

Figure 2. Fibrillation and fasciculation potentials were identified in the left deltoid muscle on needle electromyography recording. Horizontal bar 200 msec. Vertical bar 0.5.

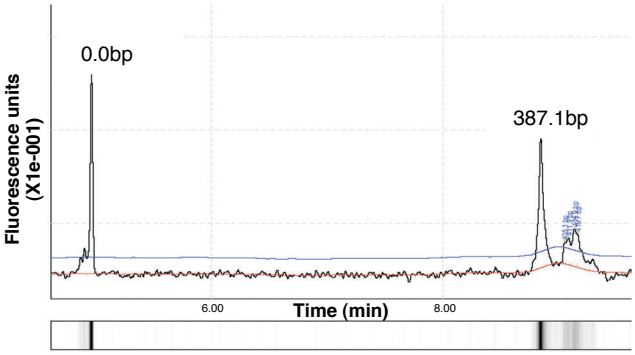

Figure 3. Capillary electrophoresis of androgen receptor gene locus. The polymerase chain reaction product containing CAG trinucleotide tandem repeats revealed 387 base pairs (bp) by the capillary electrophoresis method. The size corresponded to 67 CAG trinucleotide repeats.

DISCUSSION

Muscle weakness, fasciculation without obvious sensory deficit suggest lower motor neuron diseases or motor axonal neuropathy. A number of neuromuscular disorders can involve anterior horn cells or cause motor neuropathy[11]. The bulbar and four-limb distribution does not favor a focal lesion; the adult-onset, normal intelligence, no obvious sensory or extrapyramidal system signs also make many hereditary degenerative diseases such as certain forms of spinal muscular atrophy, spinocerebellar ataxia, Friedreich ataxia unlikely. Normal nerve conduction velocity dose not suggest motor neuropathy. The brisk tendon reflex identified in this patient, probably suggests upper motor neuron involvement; in that case, ALS, the most frequently encountered motor neuron disease that involves both upper and lower motor neurons is highly suspected. However, the relatively early onset, slow progression, negative primitive reflexes and additional non-neurologic symptoms including gynecomastia, glucose intolerance and lipid metabolism disorder favor the inherited motor neuron disease, KD. Genetic testing by PCR and CE showed expansion of a CAG trinucleotide repeat (67 CAGs) in the androgen receptor gene confirmed the final diagnosis of KD. Whether the brisk tendon reflexes found in our patient is due to the latent spinal cord involvement of KD as suspected in a recent article[12] or the coexisted cervical and lumbar spine degeneration needs later follow-up. In addition, brisk reflex changes might only suggest that the patient was in an anxious state during the neurological examination.

KD, or X-linked recessive spinal bulbar muscular

atrophy (SBMA), is a clinically and genetically distinct disorder, in which bulbar-limb girdle muscle weakness developed after adolescent-onset signs of androgen insensitivity[1]. It is caused by an abnormal increase in the CAG triplet repeats in the first exon of the androgen receptor gene. In healthy individuals, the CAG triplet repeats range from 17 to 26, whereas patients with KD have more than 40 CAG triplet repeats[13]. Our patient had 67 CAG triplet repeats. Despite there is still debate about the correlation between the length of the CAG triplet repeats and the disease severity; most studies showed an earlier onset in cases with larger CAG triplet repeats[1,13-17].

Prominence of breast tissue consistent with gynecomastia has been noted on examination. As known, the causes of gynecomastia are multiple[18]. In many cases, an imbalance between estrogen and androgen levels causes changes in cellular elements in breast tissue[18]. This could be due to a decrease in production of androgen, an increase in estrogen formation or a decreased androgen responsiveness at the breast level[1,2]. The normal ratio of estrogen to testosterone in the circulation is approximately 1:300. Although the plasma estradiol and testosterone levels are within normal limits, an elevated estrogen-to-androgen ratio (about 1:168) has been found in our patient. Thus, the gynecomastia in KD may be the combined result of a relative insensitivity to testosterone due to defective androgen receptors with an increased sensitivity of the breast tissue to a normal estrogen level, and a relativly increased estrogen-to-androgen ratio.

Reviewing the literatures, KD is most often confused with ALS[7,19]. However, recognition of KD is important because the prognosis, natural history, and management are different form those of ALS. Life expectancy is generally not reduced in patients with KD, whereas ALS progresses more rapidly with death occurring within 2 to 5 years after disease onset[7,19]. The onset of KD seems earlier than general believed, the symptoms and signs usually emerge in early adolescence, with gynecomastia, muscle pain come first, followed by muscle weakness[3,14,20,21]. Fasciculation is often generalized but not necessarily correlated with muscle weakness[1]. Our patient's clinical features were exactly the same, and he had prominent tongue atrophy but nasal tone was only mild after prolonged talking. The remarkable mismatch between the extent of the tongue atrophy and the clinical signs of dysarthria and dysphagia is a clinical hallmark of KD[1].

In conclusion, the prevalence rate of KD in Taiwan remains to be defined. KD can be mistaken for ALS[7,8], so it is prudent to check gynecomastia, androgen insensitivity in every male patient with ALS mimic syndromes[19], even if there is no obvious family history like our case. In one study, 2% of the ALS cases are actually victims of KD[19]. Accurate diagnosis of KD can now be accomplished easily and quickly by screening for the CAG repeat expansion, which also provides a good tool for genetic counseling for male patients and female carriers before marriage or conceiving a child[7,19, 22,23]. Some studies showed that testosterone conveyed neurotoxic effects in KD by translocating the mutated androgen receptor from the cytosol into the nucleus and anti-testosterone therapy with leuprorelin, induction of heat shock protein (Hsp) 70, inhibition of histone deacetylase or inhibition of Hsp 90 had potent therapeutic effects in the SBMA transgenic mice[2,3]. With the accurate diagnosis and advanced molecular studies, hopefully, KD will soon be a treatable disease.

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