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Kennedy's disease

肯尼迪病

Kennedy's disease is an X-linked, neurodegenerative disorder, characterised by lower motor neuron syndrome. This report gives the clinical details of six male patients with Kennedy's disease diagnosed at Princess Margaret Hospital. Three were initially diagnosed with other neurological diseases, with the diagnosis of Kennedy's disease made after genetic testing. This hereditary disease should be considered in male patients with muscle weakness, particularly those with a presentation suggesting atypical motor neuron disease.

肯尼迪病是與X染色體有關的神經變性紊亂，患者通常會出現下行運動神經元綜合症。本報告提供了經瑪嘉烈醫院診斷的六名肯尼迪病的男性患者的臨床資料。其中三名患者初時被診斷為患上其他神經疾病，經基因測試後才被證實患上肯尼迪病。對於肌肉虛弱的男性病人，尤其是呈非典型運動神經元疾病的患者，應考慮他們患上這種遺傳病的可能性。

Introduction

Kennedy's disease, an X-linked spinal and bulbar muscular atrophy, is a neurodegenerative disorder characterised by loss of lower motor neurons.[1-3] Patients with this disease exhibit progressive proximal and bulbar muscle weakness; atrophy, and fasciculation of limb and facial muscles; speech, swallowing, and walking difficulties; and mild sensory deficits. Gynaecomastia and infertility may also be observed. In general, patients live a normal life span, although they may become confined to a wheelchair as the disease progresses.

Kennedy's disease is caused by unstable expansion of the CAG tandem repeat in exon 1 of the androgen receptor (AR) gene, chromosome location Xq11-12.[3-5] The number of CAG repeats often exceeds 40, compared with 17-26 repeats for healthy controls.[6] Other CAG repeat diseases include Huntington's disease, spinocerebellar ataxia, and dentatorubral-pallidoluysian atrophy.[7] CAG repeats encode polyglutamine tracts and expansion of this tract presumably has a toxic gain of function effect in CAG repeat disorders.[7] An inverse correlation has been reported between the number of CAG repeats and the age of onset of muscle weakness.[8] However, other reports have shown variable phenotypic expression between and within families, unrelated to the number of repeats.[9,10] The recognition of classical Kennedy's disease is not difficult, but false positives and negatives are common as it can mimic other muscular diseases.[11-14]

Case reports

Patient characteristics and clinical findings of the six patients are summarised in the Table. The Fig shows findings on electrophoresis (on 2% agarose gel) of polymerase chain reaction (PCR) products of the AR gene for a healthy control and the six reported patients.

Case 1

A 38-year-old man had noted a slowed walking pace and proximal muscle weakness since the age of 20 years. No other family members were affected. Physical examination showed no muscle wasting or fasciculation. The bulbar muscles and extraocular muscles were normal. There was minimal proximal weakness, with shoulder abduction of 4+/5 and hip flexion of 4+/5. Reflexes were present

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Table. Characteristics and clinical findings of six patients with Kennedy's disease

Patients	Age of onset/age (years)	Offspring	Sexual function	Gynaecomastia	Known family history	NCV* testing: motor
1	20/38	One son	Decreased libido	Present	No	Prolonged distal latency
2	46/53	No children	Normal	Absent	No	Prolonged distal latency and low CMAP‡
3	40/42	One son	Normal	Absent	No	Prolonged distal latency and low CMAP
4	33/55	One son	Normal	Present	No	Normal
5	61/62	Two daughters	Normal	Absent	No	Prolonged distal latency
6	43/48	One daughter	Normal	Absent	No	Prolonged distal latency

* NCV nerve conduction velocity
† EMG electromyography
‡ CMAP compound motor action potentials
§ SNAP sensory nerve action potentials

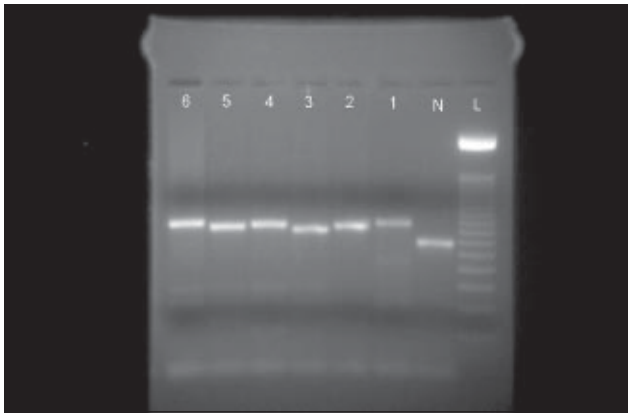

Fig. Electrophoresis on 2% agarose gel of polymerase chain reaction products of the androgen receptor gene
Lane L corresponds to the DNA ladder, N to a normal control, and 1 to 6 to patients 1 to 6. The number of CAG repeats was determined by electrophoresis on 5% polyacrylamide gel

although diminished, plantar responses were normal, and sensation was intact. Plasma creatinine kinase (CK) level was 3000 U/L (reference range, 50-200 U/L). Nerve conduction velocity testing showed an absence of response. Electromyography and muscle biopsy showed non-specific neuropathic changes only. Imaging studies of the brain and spinal cord were normal. The presumptive diagnosis was proximal spinal muscular atrophy (SMA). Seven years later, his condition continued to deteriorate and he required a quadripod to assist with walking. Screening for the homozygous deletions in exon 7 and 8 of the survival motor neuron gene was negative. Subsequent physical examination showed that he had gynaecomastia. Investigation of the CAG repeat region in exon 1 of the AR gene by PCR[13] showed an expanded CAG allele of 59 repeats. This confirmed the diagnosis of Kennedy's disease.

Case 2

A 53-year-old man had a history of angina and had complained of vague, progressive, generalised muscle weakness for 7 years. The symptoms started in his lower limbs, and exercise tolerance had deteriorated with time. There was no muscle fasciculation or gynaecomastia evident, and no family history of muscle weakness. Shoulder abduction was 4/5 and hip flexion was 4+/5 bilaterally. The plasma CK level was approximately 800 U/L. Reflexes were preserved. Nerve conduction velocity testing showed a mild, axonal-type, peripheral neuropathy and the sensory nerve conduction study was normal. Electromyography showed giant motor unit potentials over most muscle groups, with no fasciculation or positive sharp waves. Muscle biopsy was normal. A probable diagnosis of SMA or atypical motor neuron disease (MND) was given. Seven years later, PCR testing confirmed Kennedy's disease, with an expanded CAG allele of 54 repeats.

Case 3

A 42-year-old man presented with a complaint of weakness in the right upper and right lower limbs, which had insidiously progressed for 2 years. A provisional diagnosis of stroke was made. The patient's past health had been good and there was no family history of muscle weakness. Computed tomography brain scans were normal. Blood tests were normal, with the exception of plasma CK, which was 1000 U/L. Physical examination showed that right shoulder abduction was 4/5 and right hip flexion was 4/5. There were no upper motor neuron signs, and no wasting or fasciculation. Reflexes, coordination, and sensation were normal. Magnetic resonance imaging of the cervical spine did not detect any abnormalities. Six months later, the patient developed left upper and lower limb weakness and muscle fasciculation. Examination showed that right and left shoulder abduction were 2/5 and 4/5, respectively, and right and left hip flexion was 4-/5 and 4/5, respectively. Reflexes were diminished but the bilateral plantar responses were normal. There was no gynaecomastia. The patient was thought to have an atypical MND. Polymerase chain reaction testing showed the presence of Kennedy's disease, with an expanded CAG allele of 49 repeats.

Case 4

A 55-year-old man had complained of vague, generalised muscle weakness for more than 20 years. Examination showed muscle fasciculation, gynaecomastia, and atrophy of the deltoid and biceps muscles. Muscle power was mildly diminished, with shoulder abduction of 4+/5, and elbow extension of 4+/5. Reflexes and sensation were normal. The plasma CK level was 3800 U/L. Polymerase chain reaction testing confirmed Kennedy's disease, with an expanded allele of 54 CAG repeats.

Case 5

A 62-year-old man had a 1-year history of weakness. His wife had noted that he was slow in walking and had repeated falls. There was no family history of muscle weakness and

NCV testing: sensory (sural)	EMG†	Muscle biopsy	Creatinine kinase (U/L)	CAG repeats
Absence of response	Giant motor unit	Neuropathic myopathy	3000	59
Normal	Giant motor unit	Normal	800	54
Normal	Fibrillation and positive sharp wave	Neuropathic myopathy	1000	49
Normal	Normal	Neuropathic atrophy	3800	54
Decreased SNAP§	Tongue fasciculation	Neuropathic myopathy	2300	54
Decreased SNAP	Giant motor unit	Neuropathic myopathy	1400	58

the patient's health was otherwise unremarkable. Examination showed proximal weakness of both upper and lower limbs. Shoulder abduction was 4/5 and hip flexion was 4/5 bilaterally. Reflexes, including the plantar response, were normal. There was muscle fasciculation evident, but no gynaecomastia. The plasma CK level was 2300 U/L. Polymerase chain reaction testing confirmed Kennedy's disease, with an expanded allele of 54 CAG repeats.

Case 6

A 48-year-old man had a 5-year history of proximal muscle weakness. The plasma CK level was 1400 U/L. Clinical examination showed similar findings to case 5. In addition, there was bulbar involvement, with slurring of his speech. There was no gynaecomastia evident. Polymerase chain reaction testing confirmed Kennedy's disease, with an expanded allele of 58 CAG repeats.

Discussion

The incidence of Kennedy's disease in Hong Kong is unknown. It has been reported to be less than 1 in 50 000 men in other parts of the world.[4] Errors in diagnosis are known to occur, however, and misdiagnosis with other MND often occurs.[11,12] This may reflect a belief that hereditary diseases usually manifest themselves in childhood—there is a tendency to overlook the possibility of hereditary disease among adult patients.[9,13] Patients with Kennedy's disease whose presentation is atypical are particularly likely to be misdiagnosed with another muscular disease.[13,14]

The list of potential differential diagnoses for proximal muscle weakness is extensive, ranging from hypokalaemia and thyroid dysfunction, to inflammatory myopathy, MND, and hereditary muscle diseases. The clinical features in the six patients reported here were not typical presentations for Kennedy's disease. The first patient initially had subtle weakness and it was only several years later that the disease became more evident. The unilateral weakness of the third patient led clinicians to diagnose stroke and only the progressive time course made that diagnosis unlikely. Furthermore, only one of the patients had obvious bulbar involvement at the time of diagnosis.

Typically, patients with Kennedy's disease present between the ages of 20 and 50 years.[15] Perhaps due to the small sample size, no correlation between CAG repeat length and the age of onset was observed in the patients described here. The most common symptom was difficulty in walking and a tendency to fall. Usually, deep tendon reflexes are decreased and patients have muscle cramps or an action tremor. Often, after approximately 10 to 20 years, patients have difficulty in climbing stairs, and one third of patients will be confined to a wheelchair, while others will have slurring of speech and difficulty in swallowing. A markedly raised plasma CK level is a common laboratory finding. The majority of patients will have a normal life expectancy. Gynaecomastia is a useful sign but is not an essential feature—it was present in two of the six patients. Gynaecomastia can be followed by decreased libido, impotence and, eventually, testicular atrophy and infertility. Men with 28 or more CAG repeats have increased risk of impaired spermatogenesis, with a higher number of CAG repeats being associated with a greater defect in spermatogenesis.[16] Since clinical androgen insensitivity tends to appear later in life, often in patients aged 40 to 50 years, many patients may have a family and approximately 72% of reported patients have had children.[17]

No specific treatment for the disease is available. Treatment with testosterone has produced controversial results and physical rehabilitation is the main area of treatment.

Genetic counselling for patients, particularly young patients, with Kennedy's disease is a sensitive and important issue. The late onset of the disease means that there may be presymptomatic male or asymptomatic female carriers in the family. However, presymptomatic genetic testing in children is hazardous and should not be done given that the disease will manifest in late adulthood and there is no specific curative treatment.[18] The patient and the family should be well supported by the clinician, medical geneticist, and clinical psychologist. The mode of inheritance of X-linked disease should be discussed with the patient. Sons will be unaffected, while daughters will be carriers, with a 50% chance of passing the abnormal gene to their offspring.

Conclusion

The six patients reported here demonstrate that patients with muscle weakness should undergo thorough and

appropriate investigation. For middle-aged male patients with proximal muscle weakness, lower motor neuron signs, gynaecomastia, and elevated CK, it is prudent to consider Kennedy's disease in the differential diagnosis. The absence of a family history does not exclude hereditary neurodegenerative diseases. As the clinical presentation in Kennedy's disease may be atypical, the diagnosis can be missed if genetic tests are not performed.

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