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DIFFERENTIAL DIAGNOSIS BETWEEN BULBOSPINAL MUSCULAR ATROPHY – KENNEDY'S DISEASE AND AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) includes a number of disorders causing degeneration of lower and upper motor neurons and findings in the bulbar region and at least two spinal regions or UMN and LMN in three spinal regions. ALS is typically presented with bulbar or asymmetric limb weakness, loss of ability to speak, to swallow and to breathe. Kennedy disease is a form of MND that is associated with bulbar involvement and X linked recessive inheritance. The symptoms include muscular cramps, a limb-girdle distribution of muscle weakness, bulbar symptoms and distinguishing clinical features include facial and perioral fasciculations in particular. This is a case study of a 43-year- old man who suffered from recurrent muscle cramping and progressive symmetric lower extremity weakness, with a prominent fatigable component to this weakness, shoulder weakness, difficulty swallowing and facial twitching. EMNG showed widespread reinnervation changes and fasciculations in arms, legs, tongue, and thoracic paraspinals, with minimal fibrillation potentials. Motor NCS were normal or borderline in amplitude, and sensory responses were absent in upper and lower limbs. Genetic testing was positive (45 CAG). Kennedy disease may be underdiagnosed, owing in part to misdiagnosis and to the mild symptoms exhibited by some patients. The electro-physiological examinations are the key point to the diagnosis of Kennedy disease. In our case, we found the symmetric weakness, sensory abnormalities on electrophysiological testing, prominent facial fasciculations, and gynecomastia which were not characteristic of the ALS, and indicated that was one of MND syndromes such as Kennedy disease and that was confirmed by genetic testing.

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Key words: *Kennedy disease, Amyotrophic lateral sclerosis, muscular atrophy, motor neuron disease*

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Introduction

The differential diagnosis of amyotrophic lateral sclerosis (ALS) includes a number of disorders causing degeneration of lower and upper motor neurons. It is important to consider these diagnoses because the prognosis is often better and in certain situations, specific treatments may be available. (1)

ALS is defined on clinical evidence and requires both upper motor neuron - UMN (such as spastic tone, hiperreflexia, and Babiski sign) and lower motor neuron - LMN (including muscle atrophy, fasciculations and weakness) and findings in the bulbar region and at least two spinal regions (cervical, thoracic, lumbosacral) or UMN and LMN in three spinal regions. A patient with ALS typically presents with bulbar or asymmetric limb weakness, more prominent in distal than in proximal muscles. Most patients with ALS will lose their ability to control their limbs, to speak, to swallow and to breathe (1). Without mechanical ventilation, death from respiratory failure typically ensues within 3 to 5 years of the onset of symptoms. The typical age of ALS onset is 60 years. Some patients have comorbid frontotemporal dementia and strong family history - familial ALS accounts for 3 to 10 % of all ALS forms while at least 90% have none -sporadic ALS. In recent years, 14 different genes have been identified that cause various types of motor neuron disease. The best evidence for this involves the protein TDP-43 in the intraneuronal cytoplasmatic protein aggregates of

SALS and in some forms of FALS. Another example, within FALS 1 has a mutation in SOD1 (2).

ALS continues to be diagnosed and followed almost entirely on the basis of clinical findings. There is no laboratory test to prove or disapprove the diagnosis. For patients with classic presentation routine chemistries, complete blood count, serum kinases , electrophysiologic testing, and imaging studies of the spine/brain are performed. More extensive laboratory testing should be reserved or more atypical presentations (pure UMN or LMN syndromes, the disease of early onset under 40 years of age or prolonged duration, coexistent systemic illness or the presence of sensory or urinary symptoms). Diagnostic CSF biomarkers may allow for improved diagnosis of ALS, may be leading to the ability to make diagnosis definitively in early cases. Routine testing for heavy metals in the serum or urine is not indicated unless there is a high suspicion for exposure. Another laboratory study that may support the diagnosis of ALS is muscle biopsy.

Multiple studies have shown that a multidisciplinary approach may prolong survival and improve the quality of life of patients with ALS (3). Only one drug has ever been shown to prolong survival in patients with ALS: riluzole. Riluzole affects neurons by three mechanisms: inhibiting excitatory amino acid release, inhibiting events after stimulation of excitatory amino acid receptors and stabilizing the inactivated state of voltage-dependent sodium channels (3). Palliative care and symptomatic therapy play an integral part in the management of patients with ALS. That included exercises, hydrotherapy, and the drugs baclofen, gabapentin, amitriptyline when there is comorbid sleep disturbance, depression or pseudobulbar affect (4).

The motor neuron disease (MND) that may present clinically with progressive dysfunction of motor neurons are included in the differential diagnosis ALS. MND includes the spectrum of clinical syndromes that result from degeneration of upper motor neurons, lower motor neurons or both. One of the syndromes is Kennedy disease.

Kennedy disease is a form of MND that is associated with bulbar involvement and X linked recessive inheritance (5).

The disease affects only males, usually at the beginning of the third or fourth decade of life. The initial symptoms include muscular cramps, a limb-girdle distribution of muscle weakness, and bulbar symptoms. Distinguishing clinical features include facial and perioral fasciculations, in particular, which are present in more than 85 % of patients, hand tremor, and tongue atrophy associated with a longitudinal midline furrow. There is no evidence of UMN involvement and sensory examination is typically normal. Other systemic manifestations include gynecomastia in 60-90 % of patients due to elevated gonadotropin levels associated with testicular atrophy, feminization, impotence, and infertility (6). Diabetes mellitus is seen in 10-20 % of patients. Genetic testing can be performed to confirm the presence of an abnormal trinucleotide repeat expansion (CAG) in the androgen receptor gene on the X chromosome. In healthy individuals, the repeats range from 17 to 26 in this coding area, whereas in Kennedy disease, the number of repeats ranges from 40 to 65. The number of the enlarged CAG repeats is significantly correlated with the age of onset but has no correlation with severity of weakness, degree of sensory neuropathy, of gynecomastia or impotence (7).

Materials and methods

This is a case study of a 43 - year-old man who was referred for a second opinion regarding the diagnosis of ALS. He reported recurrent muscle cramping since he was 25 and progressive symmetric lower extremity weakness 4 years ago. He noted a prominent fatigable component to this weakness, with worsening associated with prolonged use of the muscles. He had noted shoulder weakness, difficulty swallowing, and facial twitching. He denied a family history of neurologic illness.

The examination has shown bifacial weakness with continuous facial fasciculations, proximal extremity weakness, areflexia, and normal sensation. There was also weakness and atrophy of the tongue, mild nasal dysarthria, and significant axial weakness with lumbar lordosis. Postural tremor was noted in the upper extremities and frequent fasciculations were observed in the arms and legs. He had gynecomastia.

Serum CK level was elevated at 1800 IU/L. EMNG showed widespread reinnervation changes and fasciculations in arms, legs, tongue, and thoracic paraspinals, with minimal fibrillation potentials. Motor NCS were normal or borderline in amplitude, and sensory responses were absent in upper and lower limbs. SEP (n. medianus) showed that cortical responses and spinograms are morphologically severe altered indicating a defect in the conduction in the central and peripheral roads SS bilaterally. SEP (n. tibialis) showed morphologically altered cortical responses with prolonged latencies. Spinograms were low volted with prolonged latencies. The finding suggests a defect in the conduction in the central and peripheral roads SS bilaterally.

Muscle biopsy showed inequality in the size of muscle fibers due to the presence of atrophic fibers with elongated, angular and rounded contours that meet in small groups. Increased core presents with centralization and rare fibers under phagocytosis. Interstitially, connective tissue was neat and vessels were with a neat wall and lumen. Genetic testing was positive for an expanded allele in CAG repeat region of the androgen receptor gene (45 CAG). MRI of the brain and spine were normal.

Conclusion and discussion

Kennedy's disease, also known as spinal and bulbar muscular atrophy (SBMA), is a rare, adult-onset, X-linked recessive neuromuscular disease with an estimated incidence of approximately 1 case in 40,000 men, but the general impression is that Kennedy disease may be underdiagnosed, owing in part to misdiagnosis and to the mild symptoms exhi-

bited by some patients. SBMA is caused by expansion of a CAG repeat sequence in exon 1 of the androgen receptor gene (AR) encoding a polyglutamine (polyQ) tract. The polyQ-expanded AR accumulates in nuclei, and initiates degeneration and loss of motor neurons and dorsal root ganglia. While the disease has long been considered a pure lower motor neuron disease, recently, the presence of major hyper-creatine-kinase (CK)-emia and myopathic alterations on muscle biopsy has suggested the presence of a primary myopathy underlying a wide range of clinical manifestations (8).

The electrophysiological examinations are the key point to the diagnosis of Kennedy disease. Electroneurography shows normal conduction velocity in peripheral nerves, but the sensory nerves usually show axonal degeneration, which causes only very mild or subclinical neurological deficits. Electromyography shows chronic anterior horn cell degeneration in skeletal muscles. The molecular genetic diagnosis was introduced in 1991 when on the abnormal expansion of CAG repeat was found in the first exon of the androgen receptor gene on chromosome X with a frequency of 100 % in the affected population. Since the progression is very slow and these patients can expect a normal life span, it is essential to this syndrome from other, often more severe diseases, such as ALS.

In our case, we found symmetric weakness, sensory abnormalities on electrophysiological testing, prominent facial fasciculations, and gynecomastia which were not characteristic of the ALS, and indicated that is one of MND syndromes such as Kennedy disease and that was confirmed by genetic testing. Various endocrine abnormalities including decreased fertility and gynecomastia are common and among the first features of KD, what was the finding in our case also.

Animal models of KD have demonstrated improvement on withdrawal of testosterone, indicating that this agonist of the androgen receptor is required for the toxic effect. Potential therapies based on testosterone withdrawal in humans have shown some promise, but efficacy remains to be proven (9).

Androgen deprivation, to gene silencing, an expanding repertoire of peripheral targets, including muscle and advancement of these strategies into the clinic, can be reasonably anticipated that the landscape of treatment options for SBMA and other neuromuscular conditions will change rapidly in the near future (10).

To date, the abnormal expansion of CAG repeat has been identified to cause nine neurodegenerative diseases including SBMA, Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA) and six forms of spinocerebellar ataxia (11). Although the causative gene varies with each disease, these polyglutamine disorders share common pathways of molecular pathogenesis, such as accumulation of abnormal proteins, transcriptional dysregulation and disruption of axonal transport (12). Additionally, several lines of evidence suggest that mitochondrial impairment and elevated oxidative stress are also implicated in the pathogenesis of Kennedy's disease (13).

Despite several therapeutic attempts made in mouse models, no effective disease-modifying therapy has been available yet, although symptomatic therapy is beneficial for the management of the weakness, fatigue and bulbar symptoms (8). The disease typically lasts at least 2-3 decades and life expectancy does not appear to be compromised (14).

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DIFERENCIJALNA DIJAGNOZA SPINOBULBARNE MIŠIĆNE ATROFIJE - KENEDIJEVE BOLESTI I AMIOTROFIČNE LATERALNE SKLEROZE

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Amiotrofična lateralna skleroza (ALS) uključuje višestruke poremećaje koji uzrokuju degeneraciju gornjeg i donjeg motoričnog neurona kao i promene u bulbarnom regionu i u najmanje dva spinalna područja ili GMN i DMN u tri spinalna područja. ALS se obično manifestuje bulbarnom ili asimetričnom slabošću ekstremiteta, gubitkom govorne sposobnosti, gutanja i disanja. Kenedijeva bolest je oblik MNB koji je povezan sa bulbarnim oštećenjem i X recesivnim naslednim oboljenjem. Simptomi uključuju mišićne spazme, mišićnu slabost ekstremiteta, bulbarne simptome, a klinički simptomi uključuju facijalnu i posebno perioralnu fascikulaciju. Ovo je studija slučaja 43-godišnjeg čoveka sa rekurentnim mišićnim spazmama i progresivnom simetrijskom slabošću donjih ekstremiteta, praćen umorom, slabošću ramenog pojasa, teškoćama gutanja i grčevima lica. EMNG je pokazao promene u inervaciji i fascikulaciji ruku, nogu, jezika i torakalno paraspinalno sa minimalnim potencijalima na fibrilaciju. Motorna brzina sprovodljivosti bila je normalna do granice amplitude, sa odsustvom senzornog odgovora gornjih i donjih ekstremiteta. Genetičko testiranje bilo je pozitivno (45 CAG). Kenedijeva bolest može da bude subdijagnostifikovana, kao rezultat propuštene dijagnoze ili kao rezultat blagih simptoma kod bolesnika. Najvažniji deo dijagnoze su elektrofiziološki pregledi. U našem slučaju pokazale su se simetrična slabost, senzorne abnormalnosti u elektrofiziološkom testiranju, facijalne fascikulacije i ginekomastija, koje nisu karakteristične za ALS, što zauzvrat ukazuje na to da se radi o nekom od MNB sindroma kao što je Kenedijeva bolest, što je potvrđeno genetskim testiranjem.

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Ključne reči: *Kenedijeva bolest, amiotrofična lateralna skleroza, atrofija mišića, bolest motornog neurona*