Arq Neuropsiquiatr 2005;63(2-A):330-331

KENNEDY'S DISEASE PHENOTYPE WITH POSITIVE GENETIC STUDY FOR KUGELBERG-WELANDER'S DISEASE

Case report

Ana P. Trentin[1], Rosana H. Scola[1], Hélio A.G. Teive[1], Salmo Raskin[2], Francisco M.B. Germiniani[1], Lineu C. Werneck[1]

ABSTRACT - We described a patient with clinical findings from Kennedy`s disease and positive genetic study for Kugelberg-Welander's disease. A 24 years old man with negative family history presented with progressive spinal and bulbar muscular atrophy and gynecomastia at the age of 14. He was clinically diagnosed as having Kennedy's disease. However, a genetic study performed later was found to be negative for this disease and was positive for Kugelberg-Welander's disease, with deletion of the exons 7 and 8 in the "survival of motor neuron" gene.

KEY WORDS: Kennedy's disease, Kugelberg-Welander's disease, genetic test.

Fenótipo de doença de Kennedy com estudo genético positivo para doença de Kugelberg-Welander: relato de caso

RESUMO - Descrevemos um paciente com achados clínicos de doença de Kennedy e estudo genético positivo para doença de Kugelberg-Welander. Homem, 24 anos e história familiar negativa, iniciou aos 14 anos com atrofia muscular espinhal de caráter progressivo com ginecomastia. Obteve diagnóstico clínico de doença de Kennedy, entretanto o estudo genético foi negativo para esta doença e positivo para doença de Kugelberg-Welander, com deleções dos exons 7 e 8 e do gene do survival of motor neuron.

PALAVRAS-CHAVES: doença de Kennedy, doença de Kugelberg-Welander, teste genético.

Although several hereditary neurodegenerative diseases, among which Kennedy's disease (KD) also known as X-linked spinal and bulbar muscular atrophy and Kugelberg-Welander's disease (spinal muscle atrophy type III), are classified as lower motor neuron disease, they usually present with strikingly different clinical features[1]. As well as that, they have distinct genetic mutations, allowing a correct diagnosis based on specific and precise laboratory testing[2,3]. We present a rare case of a patient with clinical features of Kennedy's disease, whose genetic testing was compatible with spinal muscle atrophy type III (Kugelberg-Welander's disease). We also highlight the clinical and genetic divergent features of both disorders.

CASE

A 24 years old man presented to our service complaining of muscle weakness, which started when he was 14 years old. Initially the weakness was restricted to the lower limbs, progressing to upper limbs, with a predominant proximal compromise. Over time he started complaining of cramps, muscle fasciculations in his thighs and ultimately generalized weakness. He also had reduced secondary sexual features, gynecomasthy, with a previous diagnosis of hypogonadotropic hypogonadism. This was supported by laboratory findings and testosterone therapy was initiated. His family history was negative for either neurological or endocrinological disorders. He later developed dysphonia, dysphagia and had a worsening of muscle weakness in all four limbs to such an extent that at his last visit his gait was severely impaired and he was unable to walk unaided. On neurological examination lower cranial nerves were compromised, leading to clinical findings of both dysphonia and dysphagia. He also had an asymmetric tetraparesis, with a predominant compromise of proximal muscles, leading to a grade III mus-

[1]Department of Internal Medicine, Neuromuscular Service, Clinical Hospital, Universidade Federal do Paraná, Curitiba PR,Brazil; [2]Genetika Laboratory, Curitiba PR, Brazil.

Received 27 July 2004. Accepted 17 November 2004.

Dra. Rosana H. Scola - Rua General Carneiro 181 - 80060-900 Curitiba PR - Brasil. E-mail: scola@hc.ufpr.br

cle strength in upper limbs and grade I muscle strength in lower limbs. Deep tendon reflexes were absent, there was generalized muscle atrophy, fasciculations in both tights and myopatic gait.

Laboratory work-up disclosed low serum blood levels of testosterone, FSH and LH. An electromyographic study was abnormal, with findings suggestive of both active and chronic denervation in a diffuse distribution including limbs and the tongue. Nerve conduction study was normal. A muscle biopsy was performed and it also showed signs of chronic denervation. Based on both the clinical features and abnormal laboratory results, he was then diagnosed as having KD.

A blood sample was collected and sent to genetic study. Our patient showed 26 CAG repeats within the first exon of the androgen receptor gene and disclosed a deletion of exon 7 and 8 for the survival motor neuron (SMN) gene, suggestive o spinal muscle atrophy. Those findings were confirm when tested in another different genetic laboratory. Based in the result of genetic test the patient received the diagnosis of Kugelberg-Welander's disease.

DISCUSSION

Kennedy's disease, also known as known as X-linked spinal and bulbar muscular atrophy is a rare disease that first presents with symptoms such as proximal muscle weakness, cramps, fasciculations, bulbar palsy and in a few patients, signs of peripheral resistance to androgens. It is an X-linked disease, whose genetic defect is an abnormal repeated expansion of the CAG trinucleotide at the first exon of the androgen receptor gene[1,2] .Individuals affected with KD have between 40-53 CAG repeats. Normal range is between 17-26 repeats[4]. Conversely, in Kugelberg-Welander's disease (also known as spinal muscle atrophy type III) symptoms begin during childhood, with symmetrical and proximal muscle atrophy of all four limbs, without either compromise of bulbar muscles or signs of androgen resistance. The genetic mode of transmission is autosomic recessive with a deletion of either the exons 7 or 8 of the survival motor neuron gene[5-7]. More than 95% of patients with SMA type I and II and 80% of patients with SMA type III have deletions of SMN in the telomeric copy[7].

Based on genetic findings, our patient was diagnosed as having Kugelberg-Welander's disease, even though at first his clinical features led to the diagnosis of KD, except for the unusually early onset of disease. Gynecomastia is a major clinical feature in males, suggestive of androgen resistance, and it is probably due to a genetic mutation at the androgen receptor gene. This latter finding, when combined with signs of impairment of lower motor neuron is highly specific for KD, as it was observed in our patient.

There is a handful of published reports of patients with uncommon phenotypic signs, which were later diagnosed as KD. Shaw et al. reported the case of a patient whose main clinical feature was a non-specified personality disorder, initially attributed to pre-senile dementia. Genetic testing disclosed 44 repetitions of the CAG compatible with Kennedy's disease[8]. In addition to the variant phenotypic presentations of Kennedy's disease, genetic transmission can also turn out to be abnormal. Ikezoe et al. described a family that tested positive for the genetic marker of KD, despite the fact that genetic inheritance was abnormal with an autosomic dominant pattern instead of a X-linked pattern, but without androgen receptor abnormalities[9]. Schmidt et al. in 2002 described two sisters with KD, who had an expansion of CAG at the androgen receptor gene[10].

Based in our case and other reports found in the literature, one can infer that several chromosomal changes, some of which the genetic defect remains unknown, can present with the same phenotypic findings, thus partially explaining the myriad clinical presentations of the very same disease. Molecular diagnostic testing may confirm a diagnosis and may avoid the need of more extensive investigation. Genetic advice may be provided correctly.

REFFERENCES

1. Merigglioli MN, Rowin J, Sanders DB. Distinguishing clinical and electrodiagnostic features of X-linked bulb spinal neuropathy. Muscle Nerve 1999;22:1693-1697.
2. Mariotti C, Castellotti B, Pareyson D, et al. Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: a clinical and molecular study of 30 families. Neuromuscular Disord 1999;10:391-397.
3. Kaimen-Maciel DR, Medeiros M, Climácio V, et al. Atrofia muscular bulbo espinhal recessiva ligada ao cromosomo X (doença de Kennedy): estudo de uma família. Arq Neuropsiquiatr 1998;56:639-645.
4. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH. Androgen receptor gene mutations in X-linking spinal and bulbar muscular atrophy. Nature 1991;352:77-79.
5. van der Steeger G, Grootscholten PM, van der Vlies, et al. PCR-based DNA test to confirm clinical diagnosis of autosomal recessive spinal muscular atrophy. Lancet 1995;345:985-986.
6. Crawford TO. From enigmatic to problematic: the new molecular genetics of childhood spinal muscular atrophy. Neurology 1996;2:335-340.
7. Orrell RW, Figlewicz DA. Clinical implications of the genetics of ALS and other motor neuron diseases. Neurology 2001;57:9-17.
8. Shaw PJ, Thagesen H, Tomkins J, et al. Kennedy's disease: unusual molecular pathologic and clinical features. Neurology 1998;51:252-255.
9. Ikezoe K, Yoshimura T, Taniwaki T, et al. Autosomal dominant familial spinal and bulbar muscular atrophy with gynecomastia. Neurology 1999;53:2197.
10. Schmidt BJ, Greenberg CR, Allingham-Hawkins DJ, Spriggs EL. Expression of X-linked bulb spinal muscular atrophy (Kennedy disease) in two homozygous women. Neurology 2002;10:59:770-772.