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X-LINKED SPINAL AND BULBAR MUSCULAR ATROPHY (KENNEDY'S DISEASE) WITH LONG-TERM ELECTROPHYSIOLOGICAL EVALUATION

Case report

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ABSTRACT - X-linked spinal and bulbar muscular atrophy or Kennedy's disease is an adult-onset motor neuronopathy caused by a CAG repeat expansion within the first exon of an androgen receptor gene. We report the case of a 66-year-old man, previously diagnosed with motor neuron disease (MND), who presented acute and reversible left vocal fold (dysphonia) and pharyngeal paresis, followed by a slowly progressive weakness and also bouts of weakness, wasting and fasciculation on tongue, masseter, face, pharyngeal, and some proximal more than distal upper limb muscles, associated to bilateral hand tremor and mild gynecomastia. There were 5 electroneuromyography exams between 1989 and 2003 that revealed chronic reinnervation, some fasciculations (less than clinically observed) and rare fibrillation potentials, and slowly progressive sensory nerve action potentials (SNAP) abnormality, leading to absent/low amplitude potentials. PCR techniques of DNA analysis showed an abnormal number of CAG repeats, found to be 44 (normal 11-34). Our case revealed an acute and asymmetric clinical presentation related to bulbar motoneurons; low amplitude/absent SNAP with mild asymmetry; a sub-clinical or subtle involvement of proximal/distal muscles of both upper and lower limbs; and a probable evolution with bouts of acute dennervation, followed by an efficient reinnervation.

KEY WORDS: X-linked spinal and bulbar muscular atrophy, Kennedy's disease, bulbospinal neuronopathy, motor neuron disease, amyotrophic lateral sclerosis, sensory neuropathy.

Atrofia muscular bulbo-espinal ligada ao cromossomo X (doença de Kennedy) com seguimento eletrofisiológico de longo prazo: relato de caso

RESUMO - Atrofia muscular bulbo-espinal ligada ao cromossomo X (doença de Kennedy) é uma neuronopatia motora em adultos causada por expansões na repetição CAG no gene do receptor andrógeno. Neste relato, descreve-se o caso de homem de 66 anos, com diagnóstico prévio de doença do neurônio motor (DNM) que apresentou quadro agudo e reversível de paresia de prega vocal (disfonia) e de músculos faríngeos à esquerda; posteriormente seguiram-se surtos de fraqueza lentamente progressiva, atrofia e fasciculações em língua, masseter, face, faringe e membros superiores predominantemente proximal, associada a tremor bilateral de mãos e ginecomastia leve. Foram realizadas 5 eletroneuromiografias entre 1989 e 2003 que mostraram reinervação crônica, algumas fasciculações, raras fibrilações e redução progressiva de amplitude ou ausência dos potenciais de ação dos nervos sensitivos (PANS). Técnica de PCR para análise de DNA revelou expansão anormal de repetições CAG, sendo encontrado 44 (normal, 11-34). Este caso teve apresentação clínica aguda e assimétrica relacionada aos motoneurônios bulbares; PANS ausentes ou de baixa amplitude com leve assimetria; envolvimento subclínico ou leve de músculos proximais e distais tanto de membros superiores como inferiores; e, provável evolução com surtos agudos de desnervação aguda, seguida por reinervação eficiente.

PALAVRAS-CHAVE: atrofia muscular bulbo-espinal ligada ao cromossomo X, doença de Kennedy, neuronopatia bulbo-espinal, doença do neurônio motor, esclerose lateral amiotrófica, neuropatia periférica sensitiva.

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X-linked spinal and bulbar muscular atrophy (SBMA) or X-linked bulbospinal neuronopathy (Kennedy's disease), is a rare genetic neuromuscular disorder transmitted as a recessive trait and characterized by CAG repeat expansion within the first exon of an androgen receptor gene[1,2]. Kennedy's disease is usually classified among the progressive spinal amyotrophies[3]. and is characterized by slowly progressive proximal muscle weakness, prominent muscle cramps and fasciculation, bulbar weakness and in some patients, signs of androgen insensitivity[2]. This disorder is frequently misdiagnosed as a motor neuron disease (MND) mainly in its main form, amyotrophic lateral sclerosis (ALS). Differing from the latter, SBMA is characterized by earlier age of onset, slow progression, involvement of only spinal motor neurons, exuberant bulbar symptoms, testicular atrophy and gynecomastia in some cases. Besides this, there is also asymptomatic sensory involvement detected in nerve conduction studies[4]; though, in some cases it presents signs of glove-stocking type sensory disturbance[5]. Neurophysiologists must be aware of this condition, mainly when men present greater symmetry of findings and slow progression of clear bulbar abnormalities. Electroneuromyography (ENMG) findings include large motor unit potentials (chronic reinnervation), scattered fibrillation potentials (few active dennervation) and sensory nerve action potentials (SNAP) absent or with low amplitude[3,4]

Seefeld et al.[6] in 1995 probably reported the first two cases of Kennedy´s disease in Brazil and, after that, in 1998 Kaimen-Maciel et al.[7] reported a family with 3 cases and one carrier. We now report the first well-documented long-term electrodiagnosed Brazilian case of Kennedy's disease which had a previously ALS diagnosis over almost ten years. Suspicion arose from electromyography and sensory nerve conduction abnormalities and was then confirmed genetically through CAG triplet expansion by PCR study.

CASE

A 66-year-old Caucasian man, father of three, reported a history of acute morning dysphonia in March 1993, associated with choking, swallowing and cough paresis. There was no fluctuation throughout the day. There was no dizziness or vomiting, or atrophy in any segment. The daughter observed some probable fasciculations in face and upper limbs. An otorhinolaryngology consultation revealed left vocal fold and pharyngeal paresis; after 5 months a progressive and persistent improvement occurred and he became asymptomatic except for a slight cough. In December 1995, he noted some speech disorder and this tongue seemed to be "locked and slow" worsening after emotional distress. He also presented pain in left upper limb associated to hand weakness and atrophy without any sensory complaint. Again he started a progressive improvement after several months and no further sequel.

At the beginning of 1998 he noticed that his face was atrophic, mainly in the masseter region; sporadic falling occurred while walking as well as some difficulty in buttoning his shirts. In 1999 he started presenting dysphagia and apnea crisis once a month but never severe enough to be taken to the hospital. In 2000 he noticed a slight left hand tremor and a bilateral eyelid reduction. At the end of 2002 a chewing difficulty started, mainly with solid foods like meat; choking and difficulty coughing became more frequent. In 2003 he also noticed a tremor in his right hand and worsening of the weakness in his left hand.

There were no references to other systemic diseases. In 1989 he suffered a cervical spine trauma after a car accident and a fracture on C4-C5 was detected; a slight weakness and hypotrophy in right upper limb was observed, without any restriction to his daily-life activities; surgery was not indicated. A few months ago he had a surgery for ptosis. There was no consanguinity; his ascendants were from Italy and Portugal; no other similar cases were reported in the family.

Physical examination and blood pressure were normal. Slight gynecomastia was observed without testicular atrophy. On neurological examination a slight bilateral shoulder girdle weakness was noticed, as follows: MRC was found 4/5 in neck flexors and bilaterally mainly on right, *Supraspinatus, Infraspinatus, Brachioradialis, Del - toideus, Triceps, Rhomboideus, Serratus Anterior, Biceps Brachii* and carpi and finger flexor/extension. Atrophy was also found in *Deltoideus* and *Biceps Brachii*. Hand muscles and lower limbs were normal, but MRC 4/5 in *Iliopsoas and Gluteus Maximus* was found. Fasciculations were observed in upper limbs, lower limbs, trunk, face and tongue. Muscle stretch reflexes were normal in upper and lower limbs, yet absent in biceps and brachioradialis; normal cutaneous plantar reflex was obtained bilaterally. Sensation, however, was normal. There was a palatal arch and uvula deviation to the right, mild left tongue weakness with atrophy; severe weakness with atrophy in both *Masseter* muscles and mild bilateral weakness in *Orbicularis Oculi* muscle; normal gag reflex.

Lumbar, cervical, skull basis, thoracic and larynx computerized tomography scans were normal without expansive mass or fractures, except the one described previously in C4-C5. CK was elevated (564 U/L; ULN 170).Thyroid was normal as were all other general routine blood tests.

Throughout the disease he was referred to us for ENMG in December 1989 due to cervical trauma and in May 1993, May 1998, September 1999 and July 2003 for motor neuron disease follow-up. The results are presented in Table 1 for nerve conduction studies and in Table 2 for needle

Table 1. Nerve conduction data.

		Dec 1989 R/L	May 1993 R	May 1998 R/L	Sep 1999 R	July 2003 R
Sensory						
Median	Latency (ms)	2.7 / 2.9	2.5	NR / 2.6	NR	NR
	Amplitude (uV)	10.0 / 10.0	7.0	NR / 4.0	NR	NR
	CV (m/s)	51.8 / 48.2	56.0	NR / 53.8	NR	NR
Ulnar	Latency (ms)	2.2 / 2.2	2.3	2.2 / 2.3	NR	2.32
	Amplitude (uV)	15.0 / 15.0	10.0	3.0 / 8.0	NR	6.4
	CV (m/s)	54.5 / 54.5	52.1	59.0 / 56.5	NR	51.7
Radial	Latency (ms)	1.9 / 2.0	1.5	NR / 2.0	NR	ND
	Amplitude (uV)	10.0 / 15.0	15.0	NR / 6.0	NR	ND
	CV (m/s)	63.1 / 60.0	63.3	NR / 62.5	NR	ND
Superficial peroneal	Latency (ms)	ND	ND	2.2 / ND	2.62	NR
	Amplitude (uV)	ND	ND	4.0 / ND	1.2	NR
	CV (m/s)	ND	ND	47.7 / ND	47.7	NR
Sural	Latency (ms)	ND	ND	ND	2.95	NR
	Amplitude (uV)	ND	ND	ND	3.6	NR
	CV (m/s)	ND	ND	ND	49.2	NR
Motor						
Median	Distal latency (ms)	3.6 / ND	3.7	3.9 / ND	3.89	3.63
	Amplitude (wrist, mV)	5.0 / ND	4.0	7.0 / ND	9.12	12.1
	Amplitude (elbow, mV)	5.0 / ND	4.0	7.0 / ND	7.92	10.6
	CV (elbow-wrist, m/s)	51.1 / ND	52.5	51.2 / ND	50.6	50.0
	F-wave latency	29.7 / 30.3	ND	ND / ND	ND	ND
Ulnar	Distal latency (ms)	2.6 / ND	2.6	2.6 / ND	2.68	2.54
	Amplitude (wrist, mV)	5.0 / ND	4.0	7.0 / ND	5.44	8.16
	Amplitude (elbow, mV)	5.0 / ND	4.0	7.0 / ND	5.6	7.92
	CV (elbow-wrist, m/s)	58.1 / ND	56.4	59.2 / ND	58.1	54.3
	F-wave latency	29.0 / 28.5	ND	ND	ND	ND
Peroneal	Distal latency (ms)	ND	ND	3.8 / ND	3.78	4.0
	Amplitude (ankle, mV)	ND	ND	1.2 / ND	5.0	3.6
	Amplitude (fib. head, mV)	ND	ND	1.2 / ND	ND	2.52
	CV (knee-ankle, m/s)	ND	ND	47.0 / ND	ND	44.4
Tibial	Distal latency (ms)	ND	ND	3.4 / ND	2.85	3.53
	Amplitude (ankle, mV)	ND	ND	20.0 / ND	27.2	22.2
	F-wave latency	ND	ND	49.0 / ND	ND	48.2
H-reflex	Latency (ms)	33.1 / 33.3	ND	ND	ND	ND
RNS (distal)	Decrement (3 and 5 Hz)	ND	6.2%	ND	ND	ND

R/L, right/left; ND, not done; CV, conduction velocity; NR, not recordable; RNS, repetitive nerve stimulation.

examination. After the last electrodiagnostic consultation, one of the authors (JAK), asked the patient to have a molecular study for Kennedy's disease. This suggestion was given after several neurologists had confirmed the diagnosis of ALS. In December 2003, a molecular genetic study based on PCR showed an abnormal expansion of repeat CAG in the androgen receptor gene; the CAG repeat length was found to be 44 (normal 11-34), confirming the clinical-electrophysiological suspicion of Kennedy's disease. The patient gave an informed consented for this case report.

DISCUSSION

This case reflected the difficulty of Kennedy's disease diagnosis at least in the beginning. Our study covered five ENMG studies in a 15-year follow-up from 1989, before MND (ALS) diagnosis to 2003 when

Table 2. Electromyography (needle examination).

	Dec 1989	May 1993	May 1998	Sep 1999	July 2003
Orbicularis Oculi R	ND	NE 3	NE 3.5	ND	ND
Orbicularis Oculi L	ND	NE 3	NE 3.5	ND	ND
Orbicularis Oris R	ND	NE 2.5	ND	ND	ND
Orbicularis Oris L	ND	NO 1.5	ND	ND	ND
Masseter R	ND	NE 12	ND	ND	NE 6
Masseter L	ND	NE 12	ND	ND	NE 6
Genioglossus R	ND	ND	NE 8	ND	ND
Genioglossus L	ND	ND	NE 8	ND	ND
Sternocleidomastoideus R	ND	NE 3	ND	NE 16	NE 7
Sternocleidomastoideus L	ND	NE 7	ND	NE 10	NE 7
Deltoideus R	FIB+ NE 2	ND	NE 8	FAS+ FIB+ NE 12	NE 9
Deltoideus L	ND	NE 5	NE 8	NE 8	NE 7
Infraspinatus R	FIB+ NE 2	ND	ND	ND	ND
Biceps Brachii R	FIB++ NE 3	ND	NE 8	NE 8	NE 11
Biceps Brachii L	ND	NE 5	NE 8	NE 5	NE 7
Triceps R	NO 3	ND	NE 7	NE 6	NE 17
Triceps L	ND	FIB+ NE 5	NE 8	NE 12	NE 9
Pronator Teres R	FIB+ PO 2.5	ND	ND	ND	ND
Brachioradialis R	FIB+ PO 2.5	ND	ND	NE 9	ND
Brachioradialis L	ND	ND	ND	NE 5	ND
Extensor Digitorum Communis R	PO 2.5	NE 7	ND	ND	ND
Abductor Digiti Minimi R	NO 2.5	NE 7	ND	ND	ND
Abductor Pollicis Brevis L	ND	ND	NE 8	ND	ND
I Dorsal Interossei R	ND	ND	NE 8	NE 14	NE 9
I Dorsal Interossei L	ND	ND	FIB+ NE 9	NE 9	NE 7
Vastus Lateralis R	ND	NE 7	NE 15	NE 7	NE 7
Vastus Lateralis L	ND	NE 7	NE 12	NE 7	NE 12
Tibialis Anterior R	ND	NO 2	NE 8	NE 4	FAS+ NE 8
Tibialis Anterior L	ND	NE 3	NE 4	NE 4	FAS+ NE 6
Gastrocnemius R	ND	NE 5	NE 8	NE 4	FAS+ NE 6
Gastrocnemius L	ND	NE 5	NE 8	NE 9	FAS+ NE 7

ND, not done; NE, chronic reinnervation (amplitude, mV); FIB, fibrillation potentials. FAS, fasciculation potentials; PO, polyphasic MUAP; NO, normal MUAP; MUAP, motor unit action potential

the correct Kennedy's disease diagnosis was proposed by one of the neurophysiologists. In the second ENMG (1993) the MND involving only inferior motoneuron (spinal progressive amyotrophy) diagnosis was suspected based on chronic reinnervation and mild active dennervation in at least three segments (brain stem, cervical and lumbosacral). A probable bad prognosis was discussed with the patient based on clinical and electrophysiological correlation. Many patients, including this one, had had the misdiagnosis of MND or ALS with all the personal and family problems related to the terrible prognosis of this disease in most cases. The patient told us that many neurologists, roughly speaking, gave him a life expectation of 3 years in 1993; though he has been in relatively good condition up to now (May 2004). The main clues for the correct diagnosis were the abnormal SNAP (low amplitude or absence) and also the slow rate of disease progression only affecting inferior motoneurons. Chronic reinnervation was found in cranial nerve muscles (*Orbicularis Oculi, Orbicularis Oris, Masseter, Genioglossus* and *Sternocleidomastoideus*), cervical muscles (*Infraspinatus, Deltoideus, Biceps Brachii, Triceps, Pronator Teres, Extensor Digitorum Communis, Abductor Digiti Minimi, Abductor Pollicis Brevis, I Dorsal Interossei*) and lumbosacral muscles (*Vastus Lateralis, Tibialis Anterior* and *Vastus Lateralis*). Fibrillation potentials (*active dennervation*) were found in right *Infraspinatus, Deltoideus, Biceps Brachii, Triceps, Pronator Teres and Brachioradialis muscles*) in the first ENMG study (1989). These findings could not be attributed to the cervical trauma at that time. After 1993, when motor neuron disease was suspected, fibrillation potentials were found only in left *Triceps*, left I *Dorsal Interossei* and right

Deltoideus muscles. Fasciculation potentials were found only in right *Deltoideus* and bilateral *Gas - trocnemius/Tibialis Anterior* muscles. We did not find complex repetitive discharges as emphasized by others[2]. We concluded that the needle examination main finding was chronic reinnervation not precisely related to clinical picture reflecting very slow motor neuron degeneration with effective reinnervation. Sensory nerve conduction revealed low amplitude or absent SNAP and seemed to have an axonal loss progression. An interesting finding was the asymmetry of the findings in some nerves (e.g. no response in right and low amplitude in left for median and radial nerves). In clinical practice significantly reduced SNAP amplitude in a patient with clinical features consistent with MND disease requires an explanation and any other cause, such as Kennedy's disease, should be considered[8].

Kennedy's disease is considered as a slow progressive form of MND symmetrically involving bulbar and spinal motor neurons associated with testicular atrophy and gynecomastia[2,4]. The age of onset is earlier than for most MND being between 45-50 years[2,4]. but both disorders may not have classic findings and may be misdiagnosed[4]. The CAG expansion repeat may be related to the age of onset, being earlier when there are longer lengths of repeats[4]. Although the electrophysiological findings are similar to those of MND, greater symmetry of findings and clear bulbar abnormalities are helpful in distinguishing the disorders. Some patients have low amplitude/absent SNAP without sensory symptoms either negative or positive. Needle examination shows large motor unit action potentials and scattered fibrillation potentials[4]. Early muscle cramps, fasciculations, hand tremor, elevated CK, dysarthria, dysphagia and weakness in face, tongue and proximal limb muscles, are also described to be frequent[2,9].

Kennedy's disease was studied in the province of Reggio Emilia in Northern Italy from 1980-1997. The mean incidence was 0.19 cases/100,000 for the male population; the average age at onset was 44.8 ± 10.1 and the average survival period was 27.3 ± 2.3 years. Whereas the incidence rate of Kennedy's disease was 16 times lower than that of ALS, the incidence rate of progressive bulbar palsy in the male population is only slightly higher than Kennedy's disease[10]. Because of the presence of sporadic cases or non-evident familial cases, it is appropriate to consider this diagnostic possibility in making a diagnosis of ALS in patients in whom lower motor neuron dysfunction or bulbar onset predominates[10,11].

Our patient is a 55-year-old, presenting a unilateral vocal fold and pharyngeal paresis, clinically reversible after a few months probably because of an active dennervation bout followed by an efficient reinnervation; cramps were not a main complaint; fasciculations were evident in clinical examination and scattered electrophysiologically; CK was mildly elevated. In spite of the asymmetry of the initial symptoms, further clinical follow-up had revealed a symmetric complaint. Different from literature, the needle examination had showed a diffuse chronic reinnervation in cranial nerves muscles and proximal/distal upper and lower limbs. In Brazil, the first two cases were reported by Seefeld et al.[6]; the sensory nerve conduction was normal, the muscles studied in needle examination were restricted to lower and upper limbs and no molecular genetic study was done at that time (1995). In the other hand, there were elevated CK, gynecomastia, cramps, tremor and slow progression of dennervation on lower motoneurons, typical findings in Kennedy´s disease. After that Kaimen-Maciel et al.[7] reported three cases and in only one they could find abnormal electromyography (spinal, medulla and pons motoneurons) without any details; nerve conduction was referred as normal. All three cases had gynecomastia and abnormal molecular genetic study.

Expansions of unstable trinucleotide (CAG) repeats cause at least 15 inherited neurological diseases of which Kennedy's disease was the first described[12]. It also includes oculopharyngeal muscular dystrophy and myotonic dystrophy. Because of the signs of androgen insensitivity, the androgen receptor became the candidate gene for Kennedy's disease after the disease was mapped in the region of the X chromosome in which this gene is located. The first exon of the androgen receptor contains a polymorphic CAG repeat that normally encodes 11 to 33 glutamines. In patients with Kennedy's disease, this CAG repeat is expanded to encode a lengthened polyglutamine tract of 38 to 62 residues. Patients with longer polyglutamine expansions tend to present symptoms at an earlier age[12]. The mutated protein has an expanded polyglutamine tract, forms intranuclear aggregates and mediates neurodegeneration through a toxic gain-of-function mechanism[12].

In conclusion, this long-term electrophysiological follow-up Kennedy's disease patient, apart from classical findings first showed an acute and asymmetric clinical presentation related to bulbar motoneurons; second, a sensory nerve conduction abnormality (low amplitude/absent SNAP) with

slight asymmetry; third, a sub-clinical or subtle involvement of proximal/distal muscles of both upper and lower limbs; fourth, a probable evolution with bouts of acute dennervation, followed by an efficient reinnervation.

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