

CLINICAL SCIENCE

Tremor in X-linked recessive spinal and bulbar muscular atrophy (Kennedy's disease)

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OBJECTIVE: To study tremor in patients with X-linked recessive spinobulbar muscular atrophy or Kennedy's disease.

METHODS: Ten patients (from 7 families) with a genetic diagnosis of Kennedy's disease were screened for the presence of tremor using a standardized clinical protocol and followed up at a neurology outpatient clinic. All index patients were genotyped and showed an expanded allele in the androgen receptor gene.

RESULTS: Mean patient age was 37.6 years and mean number of CAG repeats 47 (44-53). Tremor was present in 8 (80%) patients and was predominantly postural hand tremor. Alcohol responsiveness was detected in 7 (88%) patients with tremor, who all responded well to treatment with a β -blocker (propranolol).

CONCLUSION: Tremor is a common feature in patients with Kennedy's disease and has characteristics similar to those of essential tremor.

KEYWORDS: Kennedy's disease; X-linked recessive bulbosplinal neuronopathy; Spinal and bulbar muscular atrophy; Motor neuron disease; Tremor.

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INTRODUCTION

X-linked recessive spinal and bulbar atrophy, or Kennedy's disease (KD), is a rare lower motor neuron disease associated with a mutation in exon 1 of the androgen receptor gene on the long arm of chromosome X (Xq 11-12).^{1,2} The condition results from a CAG trinucleotide expansion at the 5' end of this gene of between 40 and 62 repeats (normal values between 11 and 33). The direct relationship between the size of the expansion, lower age of onset and predominance of motor symptoms has been well documented.^{3,4} KD is usually classified among progressive spinal muscular atrophies and is clinically characterized by onset in the third decade of life with fasciculations followed by slowly progressive proximal muscle weakness and wasting of the proximal and, less often, distal musculature at approximately 40 years of age. Other features include cramps on exertion, areflexia, bulbar signs, dysphagia, and, in some patients, signs of androgen insensitivity, such as gynecomastia, testicular atrophy and oligospermia. The clinical syndrome occurs in the absence of pyramidal, sensory, and cerebellar signs, suggesting a more prominent lower motor neuron involvement. The disorder is usually

compatible with a long life. Female homozygotes are generally asymptomatic but some reported cases have included much milder clinical manifestations such as occasional muscle cramps and perioral fasciculations, and hand tremor.

Tremor is rarely described in most motor neuron diseases, but may not be uncommon if a specific search is made. For instance, in spinal muscle atrophy types 2 and 3, postural tremor, sometimes linked to fasciculations, is occasionally found on examination.⁵ Additionally, a study assessing extra pyramidal features of amyotrophic lateral sclerosis found a frequency of tremor in 40% of patients, especially in those with a family history.⁵ Tremor is also a less common sign in KD.^{1-4,6-9} Currently, an extensive search is being made for an appropriate biomarker and an effective treatment for KD.^{10,11}

Here we report 10 confirmed cases of KD, in which the presence of tremor is assessed and the clinical characteristics of the disease are demonstrated using a standard assessment protocol.

METHODS

We assessed 10 male patients (from 7 different families) with a genetically established diagnosis of KD who were followed up in the neuromuscular disease and movement disorders outpatient units at the Hospital de Clínicas, Federal University of Paraná, and the private practices of two of the authors (HAGT and LCW). All patients signed an

informed consent form. Molecular genetic testing was carried out at the Genetika laboratory to determine the number of CAG repeats in exon 1 of the androgen receptor gene on the long arm of chromosome X. The normal cut-off point for repeats considered here was < 34 CAG.

Clinical assessment included demographic data such as current age, age of onset, defined retrospectively by determining the age at which the first symptom or sign attributable to KD was detected, and the presence of hand (predominantly resting, postural or intention), leg and head tremor (according to Movement Disorder Society criteria). Tremor response to alcohol and β -blockers was also assessed (propranolol in doses of 80–160 mg/day).

RESULTS

The mean patient age at onset was 37.6 years, mean number of CAG repeats 47 (41-53) and tremor (predominantly postural hand tremor) was found in 8 (80%) of the patients. Intention tremor of the hands together with postural tremor (also of the hands) was found in 4 patients; of these 4, one also had tremor of the lower limbs. One patient had postural tremor of the hands and head tremor. All patients with tremor were exposed to alcohol with a significant responsiveness detected in 7 (88%) patients who all responded to β -blockers (propranolol up to 160 mg/day). All patients had limb weakness, predominantly proximal, associated with bulbar symptoms. Fasciculations were found predominantly in the tongue, oral and cervical muscles. Gynecomastia was found in 8 patients. Table 1 shows the clinical features of KD and molecular genetic testing results in 10 patients.

DISCUSSION

In the original article by Kennedy et al.¹ published in 1968, in which 11 patients from two different families were analyzed, fine tremor of the hands was observed in 4 patients (36.4%) and the authors emphasized the presence of

Table 1 – Clinical features of Kennedy’s disease (tremor) and molecular genetic testing in 10 patients (from 7 families).

Clinical features	Patient									
	1	2	3	4	5	6	7	8	9	10
Family	1	2	2	2	3	3	4	5	6	7
Age	44	21	50	41	55	50	62	50	51	45
Age at onset*	40	19	40	35	49	44	43	39	37	30
Mean number of CAG repeats	47	45	53	41	46	53	44	47	47	47
Hand postural tremor	+	+	-	-	+	+	+	+	+	+
Hand intention tremor	-	-	-	-	+	+	+	-	+	-
Head tremor	+	-	-	-	-	-	-	-	-	-
Leg tremor	-	-	-	-	+	-	-	-	-	-
Alcohol responsiveness	+	+	NT	NT	+	+	+	+	-	+
β -Blocker treatment	+	+	-	-	+	+	+	+	-	+

*Age at onset was defined retrospectively by determining the age at which the first symptom or sign attributable to Kennedy’s disease was detected.
NT = not tested.

proximal muscle weakness of spinal and bulbar origin with generalized fasciculations, especially in the region of the chin and lips, and the absence of pyramidal signs and sensory or cerebellar involvement.

Since then, diagnosis of KD has been associated with the presence of muscle weakness and atrophy in the facial and bulbar regions (with dysarthria and dysphagia) and (proximal) limbs, together with cramps, fasciculations of the tongue, lips and perioral region and other associated characteristics such as gynecomastia, oligospermia and azoospermia.^{2-7,11,12}

It fell to Atsuta et al.⁴ in Japan to assess a large group of 223 patients with genetically established KD. The authors defined the natural history of the disease and concluded that action tremor of the hands was the earliest sign reported by patients, with a mean age of onset of 33 years, followed by muscle weakness (age of onset 44 years) and death at 65 years. Therefore, these findings show that tremor can precede weakness by several years (average 11 years). As other forms of postural tremor are more common (e.g., essential tremor), its presence is like an “unskilled sentinel” sign for KD, distracting clinicians from the final diagnosis. Rhodes et al.⁶ assessing the clinical characteristics of 57 patients with KD, found tremor in 23% of their cases.

Phenomenologically, tremors are classically classified according to their predominance related to posture of the affected limbs. This criterion divides tremors into rest predominant and action predominant. Rest tremor is considered a synonym of parkinsonian tremor as it is a cardinal feature of parkinsonism seen in Parkinson’s disease and drug-induced parkinsonism (caused by dopamine receptor antagonists, certain calcium channel blockers, etc). Action tremor is divided into postural and kinetic tremor. Although there is a significant overlap between these two forms of action tremor, a more prominent postural component is usually related to essential tremor, degenerative diseases (Wilson’s disease, fragile X permutation tremor ataxia syndrome, etc) or is drug induced (adrenergic drugs, valproate, lithium, etc). Kinetic tremor, however, is typically related to dysfunction of the cerebellum and its main afferent and efferent pathways, as found in degenerative disorders (spinocerebellar ataxias, Friedreich’s ataxia, etc) and structural lesions (vascular, multiple sclerosis, trauma, tumors, etc).¹⁴

In our Brazilian series of patients who had had KD for an average of 9.3 years, tremor was found in 8 of the 10 patients (80%). An interesting finding is that the tremor observed had clinical characteristics similar to those of essential tremor: it was predominantly of the hands, both postural and intentional and improved with alcohol and the use of a β -blocker. Leg and head tremor were found less frequently in this Brazilian series, coinciding with findings in patients with essential tremor. In light of the high prevalence of essential tremor (one of the commonest movement disorders) in the population in general, it is essential that a more detailed assessment of these patients is carried out to search for other signs and symptoms potentially related to KD.¹⁵ Also, the finding of some degree of responsiveness to propranolol indicates that the tremor found in these patients is, in part, related to central mechanisms.

In 2009 Hanajima et al.¹⁶ published a memorable study in which they carried out a neurophysiological assessment of the presence of postural tremor in eight patients with a

genetically confirmed diagnosis of KD. The authors found tremor with a frequency of 6–9 Hz in 7 patients, a prevalence similar to that of essential tremor. However, they concluded that the tremor should be classified as reflex tremors in 5 patients and mechanical tremors in 3. Their findings also suggest that the tremor found in KD must have a peripheral origin, unlike essential tremor, which has a central origin. Another interesting aspect of KD was studied by Suzuki et al.³ in 2008, who assessed 106 patients with a genetically confirmed diagnosis of the disease. The authors defined different phenotypes for the disease, including motor (classic) and sensory phenotypes (with disturbance of deep sensation, particularly vibratory sensation). They found a correlation between the size of the CAG repeat expansion and the electrophysiological findings: in general, for larger CAG repeat expansions, the motor phenotype predominated, and for smaller ones, the sensory phenotype.

CONCLUSION

Tremor is a common feature in patients with KD, and the characteristics of the tremor found in this Brazilian series of patients are similar to those of essential tremor.

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REFERENCES

- Kennedy WR, Alter M, Sung JH. Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked recessive trait. *Neurology*. 1968;18:671–80.
- Sobue G, Hashizume Y, Mukai E, Hirayama M, Mitsuma T, Takahashi A. X-linked recessive bulbospinal neuronopathy. A clinicopathological study. *Brain*. 1989;112:209–32.
- Suzuki K, Katsuno M, Banno H, Takeuchi Y, Atsuta N, Ito M, et al. CAG repeat size correlates to electrophysiological motor and sensory phenotypes in SBMA. *Brain*. 2008;131:229–39, doi: 10.1093/brain/awm289.
- Atsuta N, Watanabe H, Ito M, Banno H, Suzuki K, Katsuno M, et al. Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. *Brain*. 2006;129:1446–55, doi: 10.1093/brain/awl096.
- Hama K, Kihira T, Okawa M, Kajimoto Y, Hiwatani Y, Morita S, et al. [Amyotrophic lateral sclerosis associated with extrapyramidal symptoms or signs]. *No To Shinkei*. 2006;58:779–84.
- Rhodes LE, Freeman BK, Auh S, Kokkinis AD, La Pean A, Chen C, et al. Clinical features of spinal and bulbar muscular atrophy. *Brain*. 2009;132:3242–51, doi: 10.1093/brain/awp258.
- Lee JH, Shin JH, Park KP, Kim IJ, Kim CM, Lim JG, et al. Phenotypic variability in Kennedy's disease: implication of the early diagnostic features. *Acta Neurol Scand*. 2005;112:57–63, doi: 10.1111/j.1600-0404.2005.00428.x.
- Finsterer J. Bulbar and spinal muscular atrophy (Kennedy's disease): a review. *Eur J Neurol*. 2009;16:556–61, doi: 10.1111/j.1468-1331.2009.02591.x.
- Katsuno M, Banno H, Suzuki K, Adachi H, Tanaka F, Sobue G. Clinical features and molecular mechanisms of spinal and bulbar muscular atrophy (SBMA). *Adv Exp Med Biol*. 2010;685:64–74, doi: 10.1007/978-1-4419-6448-9_6.
- Banno H, Adachi H, Katsuno M, Suzuki K, Atsuta N, Watanabe H, et al. Mutant androgen receptor accumulation in spinal and bulbar muscular atrophy scrotal skin: a pathogenic marker. *Ann Neurol*. 2006;59:520–6, doi: 10.1002/ana.20735.
- Katsuno M, Banno H, Suzuki K, Takeuchi Y, Kawashima M, Yabe I, et al. Efficacy and safety of leuprorelin in patients with spinal and bulbar muscular atrophy (JASMITT study): a multicentre, randomized, double-blind, placebo-controlled trial. *Lancet Neurol*. 2010;9:875–84, doi: 10.1016/S1474-4422(10)70182-4.
- La Spada AR. Spinal and bulbar muscular atrophy. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. *Gene Reviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–1999 Feb 26 [updated 2006 Dec 28]. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20301508>.
- Sperfeld AD, Karitzky J, Brummer D, Schreiber H, Häussler J, Ludolph AC, et al. X-linked bulbospinal neuronopathy: Kennedy disease. *Arch Neurol*. 2002;59:1921–6, doi: 10.1001/archneur.59.12.1921.
- Teive HA, Munhoz RP, Werneck LC, Raskin S. Tremor in X-linked recessive spinobulbar muscular atrophy (Kennedy's Disease). *Mov Disord*. 2008;23:S391:1199, doi: 10.1002/mds.21990.
- Jankovic J, Fahn S. Physiologic and pathologic tremors. Diagnosis, mechanism, and management. *Ann Intern Med*. 1980;93:460–5.
- Hanajima R, Terao Y, Nakatani-Enomoto S, Hamada M, Yugeta A, Matsumoto H, et al. Postural tremor in X-linked spinal and bulbar muscular atrophy. *Mov Disord*. 2009;24:2063–9, doi: 10.1002/mds.22566.