



Highlights of Kennedy's Disease

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Letter to the Editor

Bulbar and spinal muscular atrophy, also called Kennedy's Disease (KD), is a very rare neurodegenerative disease, with onset in adult males usually in the fourth or fifth decade [1]. Kennedy disease is named after William Kennedy, MD, who described this condition in 1968 [2]. Twenty-five years ago, La Spada, et al. [3] demonstrated the genetic defect. International incidence is unknown [4], it has been estimated at 1:50,000 males [3]; however, is also believed to be under-diagnosed.

The pathogenesis of KD is the polymorphic CAG (cytosine, adenine, guanine) tandem-repeat expansion above 40 repeats in exon 1 of the androgen receptor (AR) gene on chromosome Xq11-12. In normal population the number of CAG codons usually ranges from 12 to 25, with an average size of 21-22. The polymorphism involving the CAD triplet repeat expansion of the AR gene, coding for a polyglutamine tract in the N-terminal transactivation domain of the AR protein, has been involved either in endocrine or neurological disorders. This hyperexpansion causes neurotoxicity, through misfolded protein toxicity. This disorder is characterized by death of motor neurons, mainly located in the anterior horns of the spinal cord and in the bulbar region [4]. Besides the toxicity, there is a loss of AR function [5,6]. Amato A, et al. [7] stated that genetic anticipation had not clearly been observed in KD.

The main neurological manifestations of KD are progressive muscle weakness, usually with an asymmetric distribution; and wasting of bulbar, facial and limb muscles [2]. Presenting symptoms include postural tremor, proximal flaccid weakness, dysarthria, and fasciculation, which will run a slow progressive course [8]. Some patients may also present with perioral fasciculation with variable bulbar paresis. The phenotypic features vary between asymptomatic biochemical alterations (such as creatine-kinase elevation) to severe muscle disease with bulbar involvement [2]. There may be marked phenotypic heterogeneity within an affected family; the size of CAG repeat expansion significantly influences the age of disease onset and the severity of the disorder [9].

Women carrying the mutant AR allele are clinically unaffected, and they only show, in rare cases, abnormal electromyograms and the appearance of occasional muscle cramps and tremors in advance ages [2]. It is possible that the physiological random inactivation of the X-chromosome in female may preserve at least 50% of total motoneurons, and this may be sufficient to maintain normal locomotor activity. However, in 2002, Schmidt, et al. [10] reported a study with two homozygous women for KD who did not show clinical signs of neurodegeneration. Thus the AR polyglutamine tract neurotoxicity may be activated in men by other factors, for instance the hormonal steroid testosterone [5].

The literature describes KD as a mild, late-onset, androgen resistance. With regards to this endocrine features, Dejager, et al. [1] studied 22 patients with KD. Nineteen of them showed clinical signs of partial androgen insensitivity; the most common feature was gynecomastia (mostly postpubertal), followed by under masculinization, testicular hypotrophy, or reduced fertility as defective spermatogenesis. Penis and prostate gland size were normal in all cases.

At our center, a small series of cases were recently reviewed by Valera Yepes, et al. [11]. We reported 4 cases with typical neurological presentation, consisting of slowly progressing generalized muscle weakness with atrophy and bulbar muscle involvement. In all cases reported, molecular analysis showed an abnormal CAG triplet repeat expansion in AR gene. In our series the main symptom that motivated consultation was muscle weakness and fatigability of the lower limbs. The most common non-neurological manifestation was gynecomastia, as seen in Dejager, et al. [1] study. Following gynecomastia, the most common features in our patients were reduced facial hair growth, testis hypotrophy, and decreased sexual interest.

The degree of androgen insensitivity is great enough to impair virilization or spermatogenesis, but is not great enough to impair normal male genital development. However, there may be subjects with androgen insensitivity with sufficient spermatogenesis to preserve fertility as seen in our series [11,12]; so the presence of progeny should not reduce the diagnosis suspicion.

It is important to notice that the endocrine symptoms can precede the appearance of the neurological symptoms, and thus the diagnosis of KD.

The typical hormonal profile usually associates normal or elevated serum testosterone with non-suppressed serum luteinizing hormone level [1-13]. Serum estradiol levels are often increased due to aromatization of testosterone [1-14]. Serum sex hormone binding globulin (SHBG) is increased by estradiol and decreased by testosterone, therefore is reliable biological marker elevated in males with androgen insensitivity [1].

The consistent feature of endocrinology abnormalities, coupled with the fact that they often precede neurological symptoms, should help clinicians to distinguish KD from other degenerative diseases [1-15]. Presumptive diagnosis is made upon medical history, clinical neurologic examination, blood chemical analysis (including serum creatine kinase), nerve conduction studies, evoked potentials, transcranial magnetic stimulation and muscle biopsy [2]. Diagnosis is confirmed with the identification of the molecular defect in the AR gene.

There is no established effective medical treatment except for symptomatic management [2-11]. Patients usually receive vitamin B complex, vitamin E and physiotherapy. Little information is available on regards to androgen supplementation treatment, however, recent experimental studies shown that testosterone or analogues may worsen the symptoms of bulbar and spinal muscular atrophy in the mouse model. Therefore, androgen deprivation could be a potential therapeutic option [2-16]. It is believed that nuclear translocation of aberrant AR is prevented; thereby protecting the toxic accumulation of the mutant protein of AR. Future research is needed for the development of effective and safe treatment.

In conclusion, partial or mild androgen insensitivity syndrome is a consistent feature of KD. We need to raise medical awareness of the diagnosis suspicion of KD in all adult male with progressive muscle weakness and endocrine disorders associated with or without a family history.

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Conflict of Interest

The authors have no potential conflicts of interest to declare.

Authorship

All authors have had access to the data and have contributed to writing this manuscript and accept responsibility for the scientific content of the manuscript.

References

- Dejager S, Bry-Gauillard, Bruckert E, Eymard F, Salachas F, et al. (2002) A comprehensive endocrine description of Kennedy's Disease revealing androgen insensitivity linked to CAG repeat length. *J Clin Endocrinol Metab* 87: 3893-3901.
- Finsterer J (2009) Bulbar and spinal muscular atrophy (Kennedy's disease): A review. *Eur J Neurol* 16: 556-561.
- La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* 352: 77-79.
- Sperfeld AD, Karitzky J, Brummer D, Schreiber H, Häussler J, et al. (2002) X-linked bulbospinal neuronopathy: Kennedy disease. *Arch Neurol* 59: 1921-1926.
- Palazzolo I, Gliozzi A, Rusmini P, Sau D, Crippa V, et al. (2008) The role of the polyglutamine tract in androgen receptor. *J Steroid Biochem Mol Biol* 108: 245-253.
- Amato AA, Prior TW, Barohn RJ, Snyder P, Papp A, et al. (1993) Kennedy's disease: a clinicopathologic correlation with mutations in the androgen receptor gene. *Neurology* 43: 791-794.
- Choong CS, Kempainen JA, Zhou ZX, Wilson EM (1996) Reduced androgen receptor gene expression with first exon CAG repeat expansion. *Mol Endocrinol* 10: 1527-1535.
- Larsen K, Smith TA (2005) "Jaw drop" as an atypical manifestation of Kennedy's disease. *Ugeskr Laeger* 167: 3310-3311.
- Lund A, Udd B, Juvonen V, Andersen PM, Cederquist K, et al. (2001) Multiple founder effects in spinal and bulbar muscular atrophy (SBMA, Kennedy disease) around the world. *Eur J Hum Genet* 9: 431-436.
- Schmidt BJ, Greenberg CR, Allingham-Hawkins DJ, Spriggs EL (2002) Expression of X-linked bulbospinal muscular atrophy (Kennedy disease) in two homozygous women. *Neurology* 59: 770-772.
- Valera Yepes R, Virgili Casas N, Povedano Panades M, Guerrero Gual M, Villabona Artero C (2015) Enfermedad de Kennedy y resistencia parcial androgénica. Descripción de 4 casos y revisión de la literatura. *Endocrinol Nutri* 62: 224-230.
- Galani A, Kitsiou-Tzeli S, Sofokleous C, Kanavakis E, Kalpini-Mavrou A (2008) Androgen insensitivity syndrome: clinical features and molecular defects. *Hormones (Athens)* 7: 217-229.
- Atsuta N, Watanabe H, Ito M, Banno H, Suzuki K, et al. (2006) Natural history of spinal and bulbar muscular atrophy (SBMA): A study of 223 Japanese patients. *Brain* 129: 1446-1455.
- Griffin JE (1992) Androgen resistance--the clinical and molecular spectrum. *N Engl J Med* 326: 611-618.
- Traynor BJ, Codd MB, Corr B, Forde C, Frost E, et al. (2000) Amyotrophic lateral sclerosis mimic syndromes: a population-based study. *Arch Neurol* 57: 109-113.
- Katsuno M, Adachi H, Doyu M, Minamiyama M, Sang C, et al. (2003) Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy. *Nat Med* 9: 768-773.