

Differential diagnosis in spinal and bulbar muscular atrophy clinical and molecular aspects

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Accepted 21 February 1995

Abstract

Kennedy disease is caused by an enlarged trinucleotide repeat sequence within the androgen receptor gene. We report here seven male patients with a benign motor neuron syndrome highly analogous to Kennedy disease but with a normal trinucleotide repeat.

Keywords: Motor neuron disease; Kennedy disease; Androgen receptor gene; Androgen sensitivity; Trinucleotide repeat

1. Introduction

Motor neuron disease (MND) is a heterogeneous group of disorders, some of which are hereditary. X-Linked bulbospinal muscular atrophy (Kennedy disease, KD) shares many features with the most common form of MND, amyotrophic lateral sclerosis. The former, however, can be identified on the basis of the following typical clinical characteristics: slowly progressive weakness of the limb, facial and bulbar muscles, perioral fasciculation, postural tremor, and areflexia of the lower limbs (Harding et al., 1982). Furthermore, roughly half of patients show signs compatible with reduced androgen sensitivity (La Spada et al., 1992). The genetic defect consists of an enlarged trinucleotide repeat sequence within the androgen receptor gene. In the normal population the length of this repeat varies between 13 to 30 repeats, whereas patients with KD have at least 40 repeats and at most 62 (La Spada et al., 1992).

In a cohort of 328 adult onset MND cases, we came across 7 male patients whose clinical characteristics were analogous to those of KD. As subsequent DNA analysis showed a normal trinucleotide repeat number of their androgen receptor gene, we will refer to those patients as having atypical spinal and bulbar muscular atrophy (atypical SBMA).

2. Patients

All 7 atypical SBMA patients had slowly progressive lower MND with spinal and bulbar involvement. Mean age of onset was 37 years, mean duration of symptoms was 11 years. One patient had died from bulbar complications after 14 years. Bulbar dysfunction (dysarthria or dysphagia) and/or facial weakness was present in 4/7. Perioral fasciculation was noted in 5/7 and tongue atrophy with fibrillation in 6/7. Slight pseudobulbar signs were present in 4/7. Clear upper motor neuron signs like spasticity, hyperreflexia and extensor plantar signs were absent. Site of onset of weakness was distal in 5/7 and onset was asymmetrical in 6/7. Fasciculations were present in all but one patient. Knee and

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ankle jerks were preserved in 6/7, and so was vibration sense. Postural tremor was found in 5/7 patients. Six out of 7 had signs suggestive of reduced androgen sensitivity, like gynecomastia (6/7), infertility (2/7) and diminished potency (1/7). Two patients were brothers, their family history was compatible with an X-linked mode of inheritance. The remaining 5 patients were apparently sporadic cases.

Three KD patients had a mean age of onset of 52 years and a mean duration of symptoms of 9 years. Bulbar dysfunction, facial weakness, perioral fasciculation, tongue atrophy, proximal onset, symmetrical weakness, and postural tremor were present in all. Fasciculations were noted in 2/3, vibration sense was diminished in 2/3. Knee and ankle jerks were absent in all. Two had gynecomastia. One patient had a family history suggestive of an X-linked trait, the other 2 patients were sporadic cases.

3. Additional investigations

Electrophysiological testing was carried out in 6 atypical SBMA cases. Denervation activity, fasciculations or both were present in 5/6. Normal sensory conduction velocities were recorded in 5/6 and normal sensory nerve action potentials (SNAP) in 4/6 atypical SBMA cases, whereas all three KD patients had slightly reduced sensory conduction velocities and decreased SNAPs. Conduction blocking was absent in all.

Serum creatine kinase activity was slightly increased in both groups. All patients had normal hexosaminidase A and B activities. Paraproteinemia was absent in all patients. Five atypical SBMA patients consented to detailed endocrinological testing. Estradiol was elevated in 2/5 and estrone was normal in all but one case in whom it was slightly increased. Two patients had slightly reduced resting levels of testosterone but with an adequate rise on stimulation with β -HCG. A third patient, with normal resting testosterone, showed a diminished response to β -HCG. Prolactin and response levels of FSH and LH to LHRH were normal in all patients. 17-OH-Progesterone and androstenedione were slightly elevated in one atypical SBMA case. Testing of the pituitary-thyroid and the pituitary-adrenal axes was unrevealing in all patients.

Molecular analysis showed the androgen receptor gene to contain a trinucleotide repeat number within the normal range in all atypical SBMA cases (22–24 repeats) whereas the KD patients had an expanded repeat (42–44). In the atypical SBMA cases, the entire coding sequence of the androgen receptor gene was

screened for mutations by means of single strand confirmation polymorphism analysis (Ris-Stalpers et al., 1994). Except for a silent mutation at codon 210 (AGG \rightarrow AGA) in one patient, no mutations were identified.

4. Discussion

Atypical SBMA has many characteristics in common with KD. Main differences consist of site of onset of weakness (distal and asymmetrical), preserved tendon reflexes of the legs, absence of mild sensory impairment, and in some atypical SBMA cases pseudobulbar signs. Perioral fasciculation, postural tremor or signs suggestive of reduced androgen sensitivity in a MND patient with a benign course do not differentiate between KD and atypical SBMA.

Abnormalities of the pituitary-gonadal axis in MND are not restricted to KD, e.g. elevated values of estrone have been reported in ALS and Kugelberg-Welander SMA (Usuki et al., 1989). Although a particular pattern in atypical SBMA is lacking, our results confirm the presence of pituitary-gonadal abnormalities in MND. The significance of those abnormalities remains elusive.

The present series shows the usefulness of DNA analysis in differentiating mimicking disorders. Mutation analysis contributes to a finer delineation of KD, thus making atypical SBMA available for further study.

Acknowledgements

Supported in part by grants from the Schuhmacher-Kramer Foundation and the Prinses Beatrix Fonds.

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