Kennedy Disease

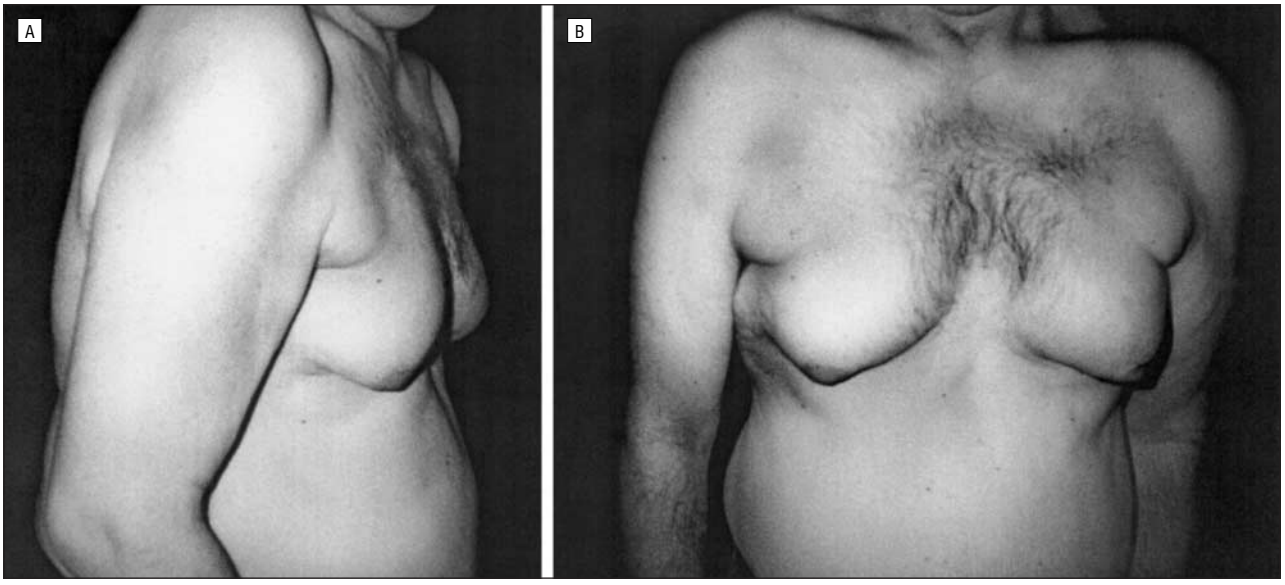
Avoiding Misdiagnosis

A 51-YEAR-OLD man with a history of prominent muscle cramps and adult-onset diabetes mellitus was seen for slowly progressive muscle weakness and atrophy predominantly affecting the proximal shoulder girdle muscles. He had no bulbar symptoms, but tongue, facial, and, particularly, perioral fasciculations were prominent. He had modest sensory disturbances, and his tendon reflexes were markedly depressed, findings that were attributed to diabetes mellitus neuropathy. Careful family history assessment revealed numerous neurologically healthy relatives with diabetes mellitus but no family history of Kennedy disease or any similar phenotype.

The initial diagnosis was amyotrophic lateral sclerosis (ALS) with predominantly lower motor neuron involvement. However, clinical reassessment revealed gynecomastia (**Figure**). He had no testicular atrophy, and the development of his primary and secondary sexual characteristics was normal. He had a healthy 22-year-old son. Serum androgen and estrogen levels were within reference limits. Creatine kinase levels were 5 times the upper limit of normal. The diagnosis of Kennedy disease was established by polymerase chain reaction analysis that showed an enlargement of the CAG repeat sequence, with 43 CAG triplet repeats in the androgen receptor gene on the X chromosome.

COMMENT

Kennedy disease,[1] or X-linked recessive bulbospinal neuronopathy, is a clinically and genetically distinct disorder caused by an abnormal increase in the CAG triplet repeat in the first exon of the androgen receptor gene. In healthy individuals, the CAG triplet repeats range from 17 to 26, whereas patients with Kennedy disease have more than 40 CAG triplet repeats, with no overlap between the control and patient groups.[2] Kennedy disease is characterized by the loss of lower motor neurons, but, unlike ALS, the upper motor neurons are not affected. Patients with Kennedy disease exhibit progressive weakness, muscle cramps, atrophy, and prominent fasciculations of limb and facial muscles, all resembling ALS syndromes. This occasionally makes an accurate diagnosis difficult, and previous studies have identified patients carrying the Kennedy disease mutation who have been misdiagnosed as having progressive spinal muscular atrophy[3] or ALS.[4] Recognition of this disorder in men is important because prognosis, natural history, and management are different than those of ALS



Patient with Kennedy disease. Note the wasting of the proximal upper arm and shoulder girdle muscles and gynecomastia.

and other lower motor neuron syndromes. Life expectancy is generally not reduced in patients with Kennedy disease, whereas ALS progresses more rapidly, with death occurring within 2 to 5 years of onset. Genetic counseling is important for patients, male siblings, and potential carriers of the disease.

In conclusion, the absence of a family history is insufficient to exclude the diagnosis of Kennedy disease, and men diagnosed as having an atypical form of ALS or a motor neuron disease who lack upper motor neuron symptoms and signs must be screened for the CAG repeat expansion.

Konstantinos Paparounas, MD, PhD
Department of Internal Medicine
Hatzikosta General Hospital of Ioannina
Makrygianni Avenue
Ioannina 45001
Greece
(e-mail: kostpap@otenet.gr).
Anna Gotsi, MD
Köln, Germany
Maria Syrrou, PhD
Nikolaos Akritidis, MD
Ioannina

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