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ABNORMAL EYE MOVEMENTS IN KENNEDY DISEASE

Kennedy disease, also known as spinal and bulbar muscular atrophy, is a neurodegenerative disease affecting lower motor neurons.¹ The underlying genetic abnormality, a triplet (CAG) repeat expansion in the androgen receptor gene on the X chromosome, produces a toxic polyglutamine expansion in the androgen receptor protein.² The disease is characterized by slowly progressive proximal muscle atrophy, weakness, and fasciculations, with prominent bulbar involvement, tremor, and, reportedly, sparing of eye movements.^{1,3,4} Stigmata of androgen insufficiency, such as gynecomastia, may be present.³ We report a patient with genetically confirmed Kennedy disease who had abnormal eye movements.

Case report. A 58-year-old Caucasian man with a history of dyslipidemia and bilateral retinal detachments presented with progressive onset of proximal muscle atrophy, weakness, fasciculations, and tremor over 20 years. He also reported a progressive decline in mobility and fine motor control, as well as dysarthria and dysphagia. He denied sensory symptoms, sphincter disturbance, or visual symptoms, such as diplopia.

On examination, there was atrophy of facial, bulbar, and limb muscles. Perioral, tongue, and limb muscle fasciculations were noted. There was moderate weakness of facial, palatal, tongue, and proximal limb muscles, with milder weakness of distal limb muscles. The reflexes were depressed and the plantar responses flexor. There were no cerebellar signs. Mild distal sensory loss was noted in the lower limbs. Visual acuity and color vision were within normal limits. Visual fields were full to confrontation. There was no optic atrophy, and his pupillary responses were normal. Ocular motor examination revealed a small exophoria, no nystagmus, and full ductions and versions. Horizontal saccades were disconjugately slowed, more so for the adducting than abducting eye (video on the *Neurology*[®] Web site at www.neurology.org). Vertical saccades were conjugately slowed in both directions (video), whereas vestibular-evoked, pursuit, and vergence eye movements were clinically normal. Gynecomastia was noted, without any other signs of androgen insufficiency.

Eye movement recordings using the magnetic search coil technique⁵ confirmed that horizontal saccades were abnormally slow compared with those of normal subjects, with adducting saccades being

slower than abducting saccades (figure, A and C). Vertical saccades were also mildly slowed, but conjugate (figure, B and D), whereas pursuit and vergence eye movements were normal. Vestibular-evoked eye movements in response to high-acceleration horizontal head rotations were disconjugately slowed, with adducting eye movements being slower than abducting eye movements.

Nerve conduction studies showed globally decreased sensory nerve action potentials, while electromyography showed chronic neurogenic changes with rare fibrillations. Serum creatine kinase was increased (395 U/L). Brain MRI revealed scattered nonspecific periventricular and subcortical white matter changes; no areas of signal increase were seen in the brainstem. Visual evoked potentials (VEPs) were prolonged. Genetic studies revealed an increased CAG repeat number (47; normal <40) in the androgen receptor gene, confirming the diagnosis of Kennedy disease.

Discussion. Prior descriptions of the Kennedy disease phenotype in large patient cohorts suggest that eye movements are spared, even late in the disease.^{1,3,4} Our patient's clinical findings were typical for Kennedy disease, although he also had asymptomatic disconjugate slowing of horizontal saccades and vestibular-evoked eye movements, with mild conjugate slowing of vertical saccades. Given the presence of the white matter changes and prolonged VEPs, multiple sclerosis was considered but thought unlikely, as both the clinical course and slowed saccades were atypical for multiple sclerosis⁵; prolonged VEPs have been reported in patients with Kennedy disease and are possibly consequent to abnormal androgen receptor function in the visual pathways.⁶

Slow saccades can result from lesions affecting extraocular muscles, their motor neurons, or prenuclear (saccadic burst) neurons in the brainstem reticular formation.⁵ Slowing of our patient's vestibular-evoked eye movements suggests involvement of ocular motor neurons rather than prenuclear neurons. Furthermore, relative slowing of adducting eye movements suggests internuclear ophthalmoplegia, implying greater involvement of internuclear neurons than abducens motor neurons.

Postmortem histopathologic studies of cohorts with Kennedy disease have demonstrated relative sparing of neurons in the third, fourth, and sixth brainstem nuclei, whereas there is severe neuronal depletion in other brainstem motor nuclei.^{1,7} Furthermore, histologic studies of rodent brainstem sec-

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Figure Search coil recordings of horizontal and vertical saccades

(A) Time series of eye position (upper panel) and velocity (lower panel) during 40° amplitude horizontal saccades shows disconjugate slowing. During the rightward saccade, the peak velocity of the left eye (blue line) is less than that of the right (pink line), whereas during the leftward saccade, the peak velocity of the right eye is less than that of the left. (B) Time series of eye position and velocity during 40° amplitude vertical saccades shows mild conjugate slowing. (C) Plots of saccade amplitude vs saccade peak velocity for different amplitude horizontal saccades show disconjugate slowing when compared with the mean (white line) and 95% prediction intervals (light blue shading) for a group of normal subjects. During rightward saccades (upper panel), the peak velocity of the left eye (blue triangles) is consistently less than that of the right (pink triangles), whereas during leftward saccades (lower panel), the peak velocity of the right eye is consistently less than that of the left. (D) Plots of saccade amplitude vs saccade peak velocity for different amplitude vertical saccades show mild conjugate slowing when compared with the mean (white line) and 95% prediction intervals (light blue shading) for a group of normal subjects. The degree of slowing for the upward saccades (upper panel) is similar to that for the downward saccades (lower panel).

tions have revealed that, while there is a large number of androgen-concentrating cells in the facial and hypoglossal nuclei, there are relatively few in the ocular motor nuclei.⁸ While these observations account for the relative sparing of eye movements in Kennedy disease, our observations suggest that eye movements can be abnormal, without causing symptoms, due to involvement of ocular motor neurons, and possibly internuclear neurons. We suggest that eye movement recordings should be performed when assessing for ocular motor involvement in clinical studies of this disease and, furthermore, that study of the ocular motor abnormalities might provide additional insights into its pathophysiology.

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