Kennedy’s Disease: A Second Genetically Confirmed Report from India

Dear Sir,

Kennedy’s disease or spinal and bulbar muscular atrophy (SBMA) is a rare, X-linked trinucleotide repeat expansion-related hereditary degenerative condition affecting the lower motor neurons due to Cytosine, Adenine, Guanine (CAG) repeat expansion on the first exon of the androgen receptor (AR) gene on Xq11-12. The true prevalence is underestimated due to reduced awareness of the disease. There has been only one genetically proven case of SBMA reported from India. The disease mainly affects males; asymptomatic women transmit the disease and a minority of female carriers (≥38 CAG repeats) report mild symptoms such as cramps or tremor. The age of onset is from 30 to 50 years. Phenotypic variability is reported in a few families wherein the age of presentation, symptoms and severity vary. We report a case of a 63-year-old man with progressive lower motor neuron syndrome with bulbar involvement, gynaecomastia and fasciculations of limb and face, electrophysiological evidence of sensory neuropathy and family history in younger brother and sister with onset in first decade. There was phenotypic variability in the same generation. Polymerase chain reaction showed 43 CAG repeats on androgen receptor gene.

A 63-year-old man presented with a history of insidious onset and gradually progressive asymmetric-onset weakness and thinning of both upper and lower limb of 18 years duration. The age of onset was around 45 years. He had twitching of muscles of the thigh, upper arm, calf and face. He developed both upper limb postural tremors since last 10 years. He developed nasal regurgitation to the liquids for the last 5-6 years and regurgitated solids for the last 2-3 years. He required one person support to get up from the bed and for ambulation. There were no sensory disturbances, cerebellar, bowel, bladder or autonomic symptoms. There was no history of infertility. There was family history in younger brother and sister. The siblings had difficulty in walking since late first decade. They were not able to run and had dysarthria. The brother died at the age of 30 years due to rabies, and the sister died at 34 years following the complications of childbirth. Systemic examination showed gynaecomastia with normal testicular size. Neurological examination showed normal cognition, slurred speech with nasal twang, bilateral lower motor neuron type of facial palsy with facial fasciculations [Figure 1a and b], sluggish palatal lift and furrowed atrophic tongue with fasciculations. Motor examination showed limb muscle weakness (proximal and
It was reclassified as X-linked bulbospinal neuropathy. This is a trinucleotide repeat (CAG) expansion in Kennedy's disease shows diffuse denervation and sensory neuronopathy in addition to motor neuron loss by Harding AE et al. in 1982.[4] The disease has X-linked recessive pattern of inheritance suggesting males are disease manifesters with females being asymptomatic carriers (majority) and mildly symptomatic in minority of cases. Inactivation of the affected X chromosome, low levels of circulating androgens and androgen receptor stimulation are the contributory factors for asymptomatic female carrier state. Kennedy's disease is frequently mistaken for amyotrophic lateral sclerosis as the muscle weakness, atrophy with fasciculations is the predominant manifestations of Kennedy's disease. The disease has non-motor manifestations like gynecomastia, testicular atrophy, erectile dysfunction, sensory symptoms in distal limbs, diabetes, hyperlipidemia, obstructive sleep apnea and Brugada syndrome.[5] Electrophysiological tests in Kennedy's disease shows diffuse denervation and sensory neuropathy. This is a trinucleotide repeat (CAG) expansion disorder with toxic androgen-dependent gain of function by the androgen receptor.[6] A phenomenon of anticipation does exist wherein there is an inverse correlation between the number of CAG repeats and age of disease onset. This is the second genetically proven case of Kennedy's disease from India. The novelty of this case is the variation in the age at presentation and phenotypic variability in the siblings (both genders affected). We want to emphasize that if the clinical features suggest Kennedy's disease, even if a female family member is affected, a clinician should not hesitate to perform the genetic test for Kennedy's disease. The examination of both siblings was not possible as they were deceased. The majority of the brain imaging findings reported are non-specific, and MRI has shown cerebral white matter changes. Atrophy of cervico-dorsal cord was reported by Sperfeld AD et al. (2005).[7] Our patient had cervicodorsal cord atrophy.

Kennedy's disease mainly affects males. It shows variability in the age of presentation and phenotypic presentation. There is single report of genetically confirmed Kennedy's disease from India. This case highlights the uncommon features of Kennedy's disease in the form of the variation in the age at presentation and phenotypic variability in the siblings.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

Figure 1: (a) Gynaecomastia (white arrow); (b) Furrowed atrophic tongue (white arrow); (c) Spine MRI sagittal view showing cervico-dorsal atrophy (white arrow)

distal; medical research council grade 3/5), wasting of all limbs with arm and thighs' fasciculations and minipolymyoclonus. He had postural tremors of both upper limbs. Sensory examination was normal. All tendon reflexes were sluggish and absent ankle jerk. Plantar responses were mute. Complete blood counts, renal, liver, thyroid function tests, creatine kinase, ammonia, lactate, vitamin B12 and serum homocysteine levels were normal. Serum testosterone levels were normal. Nerve conduction studies showed decreased compound motor action potentials with normal latency and nerve conduction velocity in all the sampled nerves and absent sensory nerve action potentials in all the sampled nerves (median, ulnar, radial, sural and superficial peroneal nerve). Electromyogram of muscles of cervical, thoracic and lumbar segment showed chronic denervation. Magnetic resonance imaging (MRI) brain and spinal cord showed cervical and dorsal cord atrophy [Figure 1c]. Ultrasonography of breasts showed retro areolar glandular enlargement of breast tissue. Polymerase chain reaction showed 43 CAG repeats (normal range: 9–36) on androgen receptor gene.

Kennedy’s disease was first described by William R. Kennedy in 1968.[1] It was reclassified as X-linked bulbospinal neuronopathy suggesting a sensory neuronopathy in addition to motor neuron loss by Harding AE et al. in 1982.[4] The disease has X-linked recessive pattern of inheritance suggesting males are disease manifesters with females being asymptomatic carriers (majority) and mildly symptomatic in minority of cases. Inactivation of the affected X chromosome, low levels of circulating androgens and androgen receptor stimulation are the contributory factors for asymptomatic female carrier state. Kennedy’s disease is frequently mistaken for amyotrophic lateral sclerosis as the muscle weakness, atrophy with fasciculations is the predominant manifestations of Kennedy’s disease. The disease has non-motor manifestations like gynecomastia, testicular atrophy, erectile dysfunction, sensory symptoms in distal limbs, diabetes, hyperlipidemia, obstructive sleep apnea and Brugada syndrome.[5] Electrophysiological tests in Kennedy’s disease shows diffuse denervation and sensory neuropathy. This is a trinucleotide repeat (CAG) expansion disorder with toxic androgen-dependent gain of function by the androgen receptor.[6] A phenomenon of anticipation does exist wherein there is an inverse correlation between the number of CAG repeats and age of disease onset. This is the second genetically proven case of Kennedy’s disease from India. The novelty of this case is the variation in the age at presentation and phenotypic variability in the siblings (both genders affected). We want to emphasize that if the clinical features suggest Kennedy’s disease, even if a female family member is affected, a clinician should not hesitate to perform the genetic test for Kennedy’s disease. The examination of both siblings was not possible as they were deceased. The majority of the brain imaging findings reported are non-specific, and MRI has shown cerebral white matter changes. Atrophy of cervico-dorsal cord was reported by Sperfeld AD et al. (2005).[7] Our patient had cervicodorsal cord atrophy.

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Rutul Shah, Rohan Mahale, Hansashree Padmanabha, Pooja Mailankody
Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India

Address for correspondence: Dr. Rohan Mahale, Department of Neurology, NIMHANS, Bangalore - 560 029, Karnataka, India. E-mail: rohanmahale83@gmail.com

REFERENCES
1. 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.
2. Dubey A, Jain R, Sodani A, Chouksey D. A case of Kennedy’s disease from India. Ann Indian Acad Neurol 2017;20:163-4.
3. Mariotti C, Castellotti B, Pareyson D, Testa D, Eoli M, Antozzi C, et al. Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: A clinical and molecular study of 30 families. Neuromusc Disord 2000;10(6):391-7.
4. Harding AE, Thomas PK, Baraitser M et al (1982) X-linked recessive bulbospinal neuronopathy: A report of ten cases. J Neurol Neurosurg Psychiatry 45:1012–9.
5. Breza M, Koutsis G. Kennedy’s disease (spinal and bulbar muscular atrophy): A clinically oriented review of a rare disease. J Neurol 2019;266:565-73.
6. Li M, Miwa S, Kobayashi Y, Merry DE, Yamamoto M, Tanaka F, Doyu M, Hashizume Y, Fischbeck KH, Sobue G. Nuclear inclusions of the androgen receptor protein in spinal and bulbar muscular atrophy. Ann Neurol 1998;44:249-54.
7. Sperfeld AD, Bretschneider V, Flaith L, Unrath A, Hanemann CO, Ludolph AC, Kassubek J. MR-pathologic comparison of the upper spinal cord in different motor neuron diseases. Eur Neurol. 2005;53:74-7.

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