



Kennedy's disease: an under-recognized motor neuron disorder

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Abstract

Kennedy's disease or spinal bulbar muscular atrophy is a rare, inherited and slowly progressive multisystem disease mostly manifesting with a motor neuron disease phenotype leading to disability. The slow progression, partial androgen insensitivity, electrophysiological evidence of sensory neuropathy, and relatively spared central nervous system pathways help differentiate it from amyotrophic lateral sclerosis. To date, there is no treatment or cure with clinical care mainly focused on accurate diagnosis, symptom management, patient education, and genetic counselling.

Keywords Kennedy's disease · Spinal bulbar muscular atrophy · Motor neuron disease

Introduction

Kennedy's disease or spinal bulbar muscular atrophy was first described by Kennedy et al. in (1968). It is a slowly progressive multisystem disorder predominately affecting the peripheral nervous system [1]. It is an inherited X-linked mutation of the androgen receptor gene with males usually affected but rarely females may exhibit some mild symptoms (such as cramps). The slowly progressive disease course of lower motor neuron dysfunction in this rare disorder leads to the frequent misdiagnosis as amyotrophic lateral sclerosis (ALS). Parboosingh et al. reported that 2% of patients diagnosed with sporadic ALS actually suffer from Kennedy's disease [2]. The disease spectrum encompasses in addition to the hallmark of progressive motor deficit, other manifestations such as sensory neuropathy and hormonal dysregulation (infertility, gynecomastia) which is often times unnoticed or unlinked to the primary symptoms [1, 3].

Etiology and pathophysiology

Kennedy's disease is the only X-linked polyglutamine disease caused by an expansion in CAG triplet repeats (> 38 repeats) leading to the formation of an abnormal protein [4]. This disorder has a remarkable phenomenon of genetic anticipation where longer triplet repeats lead to a longer polyglutamine expansion causing earlier disease onset with worse clinical manifestation. This pathologic process is caused by a mutation on the first exon of the androgen receptor (regulator of transcription) where a CAG triplet repeat is found [5]. The abnormal androgen receptor is expressed in several central nervous system loci modulating the hypothalamic–pituitary–gonadal axis pathways, as well as in the peripheral nervous system including the anterior horn cells and to a lesser extent the dorsal root ganglia and sural nerves [6, 7]. The latter explains the sensory manifestations found in some patients with Kennedy's disease. The extensive expression of androgen receptors in motor neurons is related to their role in promoting the growth and regeneration of nerves, their structures, specifically in axonal elongation. This is supported by the androgenic effects observed in animal studies conducted on the motor spinal nucleus of the bulbocavernosus muscle [8].

Hormonal dysregulation, caused by androgen insensitivity, occurs due to loss of androgen receptor function without cellular death (loss of function mechanism). On the other hand, mutant gain of function mechanism is the one responsible for neuronal cell death [9, 10]. The latter mechanism (gain of function) leads to the production of a mutant

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protein which forms nuclear and cytoplasmic aggregates (cytoplasmic aggregates also called neutrophil aggregates). Such inclusions are seen in other neurodegenerative disorders and may be considered a cardinal pathologic sign of all polyglutamine diseases [11]. Those aggregates, originally presumed toxic contributors leading to disease progression, were later proposed to play a protective role by dismantling and disposing these pathogenic proteins in closed inclusions. Other hypotheses in relation to cellular dysfunction and death from gain of function include DNA injury, mitochondrial dysfunction, endocytosis microtubule dysregulations and others [12].

Though Kennedy disease is considered a motor neuron disorder, findings on muscle biopsies also suggest a primary skeletal muscle involvement (muscle fiber hypertrophy, mitochondrial dysfunction, mitophagy, and elevated serum creatine-kinase (CK) levels) along with the expected neurogenic changes [13–16].

Prevalence and clinical manifestations

It is difficult to estimate the exact prevalence of Kennedy's disease since it is rare with variable incidence across different populations, in addition to the frequent under-recognition and possibly misdiagnosis. The 2-latter reasons are supported by the high prevalence (13 out of 85,000 male

inhabitants) reported in a district in Western Finland overshadowing the number of ALS cases in the same district [17]. The prevalence of Kennedy's disease in an Italian region as of 2018 was lower than that of the Finnish study (2.58/100,000) but relatively comparable to the prevalence of ALS in another Italian region estimated 7.85/100,000 as of 2014 [18, 19]. One should not neglect the Founder effect as one reason for such variability in the incidence of this genetic disorder in different geographical settings. In addition, the very slowly progressive course of this disease influences its epidemiology by increasing its prevalence.

As stated earlier, Kennedy's disease is a slowly progressive disorder that affects a predominantly male population. The average age at onset is around 42–43 years of age across several cohorts from different countries with a very wide range from childhood up to the seventh decade [16, 20, 21]. This data may be biased by the relatively insidious onset and absence of prominent motor manifestations at disease onset. The clinical manifestations can be divided into motor and non-motor manifestations (Table 1). The motor manifestations are restricted to the lower motor neurons and include progressive weakness, depressed deep tendon reflexes, muscle atrophy in addition to fasciculations. The proximal and distal muscles in the upper and lower extremities are equally affected but the pattern of involvement is usually asymmetric, with a tendency to affect more the dominant side [22]. The presence of signs of upper motor neuron

Table 1 Manifestations and diagnostic findings in Kennedy's disease

Neurological manifestations (according to system involvement)	Non-neurological manifestations
Lower motor neuron disorder Weakness, muscle atrophy (including tongue), cramps, fasciculations, dysarthria, dysphagia, dysphonia, muscle atrophy, quivering chin, tremor	Gynecomastia Decreased facial hair growth Decreased libido Erectile dysfunction Sterility Testicular atrophy
Myopathy Weakness, cramps, muscle atrophy, postural tremor, fatigue, myalgias	
Sensory neuropathy Numbness, tingling, parasthesias	
Central nervous system Postural and kinetic tremor, jaw tremor, memory dysfunction, poor sleep quality, sleep apnea	
Diagnostic testing	Diagnostic testing
Neurophysiological testing Inactive chronic generalized axonal polyneuropathy Sensory poly-neuronopathy Abnormal somatosensory evoked potentials Spared motor evoked potentials	Elevated CPK Elevated fasting glucose Elevated serum cholesterol, low-density lipoproteins, and triglycerides levels Azospermia, or sterility ECG abnormalities (including Brugada-type ECG)
Elevated CPK	Genetic testing
Sleep studies Sleep apnea, REM sleep without atonia, reduction in sleep quality, periodic limb movement	CAG trinucleotide repeat expansion (≥ 38)
Muscle biopsy Evidence of myopathy and neuropathy	

involvement should always point towards an alternative diagnosis. Cramps and postural tremor (particularly involving the upper extremities) may be the first symptoms experienced by patients often preceding the onset of weakness [22, 23]. Perioral fasciculations and tongue atrophy can also be found on initial presentation in up to 76% of patients, with the quivering chin sign being a cardinal sign along with gynecomastia in the setting of a motor neuron disorder presentation [24, 25]. Other initial manifestations reported include gynecomastia, excessive fatigue, muscle pain, stiffness, and sleep disturbances [26]. Bulbar manifestations including dysphagia, dysphonia, and dysarthria are usually present much later, and they are typically very slowly progressive in comparison to ALS [21, 27]. The central nervous system non-motor manifestations are less prominent and may include clinically evident as well as subclinical features. Of these, the most common is the postural and kinetic hand and/or jaw tremor (mentioned above), and neuropsychological deficits that can be documented on neuropsychological assessment predominantly affecting the frontotemporal functions including verbal and non-verbal fluency, concept formation and short/long-term memory functions [28]. Sleep disorders are common in patients with Kennedy's disease with a high prevalence of obstructive sleep apnea and REM sleep without atonia, reduced sleep quality, and presence of periodic limb movement. These disorders are the result of bulbar weakness and neurodegeneration in the brainstem sleep circuitries [29].

Sensory manifestations such as numbness and tingling sensation usually appear distally and late in the disease, but subclinical signs of both small fiber and large fiber sensory neuronopathy can be detected much earlier on nerve conduction studies as well as nerve biopsy [7, 30]. Postural instability and falls also attributed to sensory system dysfunction related to posterior column involvement can be detected on evoked potential studies [31–33]. Subclinical autonomic nervous system involvement is also reported but to a lesser extent [34].

As mentioned above, KD may exhibit signs and symptoms of endocrinological dysfunction in up to 80% of cases due to partial androgen insensitivity. Of these, gynecomastia is the most common manifestation (73% of cases) with decreased libido, erectile dysfunction, and decrease facial hair growth reported by about half of these patients. Azospermia, sterility, and testicular atrophy is less frequently reported [35]. Other features of metabolic dysfunction include high fasting glucose as well as high levels of serum cholesterol, low-density lipoproteins, and triglycerides levels [16, 35]. Data concerning cardiac disorders in KD are conflicting. In 1 study, they included 25 patients that showed no signs of cardiac involvement [36]. However in another study, abnormal ECG findings including Brugada-type ECGs was reported in nearly half of patients recruited [37].

Diagnostic studies

Electrophysiological study is usually the first testing modality applied to any patient presenting with a lower motor neuron pattern of weakness, including those with KD. This can help localize the lesion(s) level and identify the electro-clinical syndrome complementing the clinical diagnosis. KD has its own electrodiagnostic picture that includes a relatively inactive and chronic slowly progressive motor axonal polyneuropathy with evidence of sensory polyneuropathy. Needle electromyographic examination reveals chronic neurogenic changes along with a relatively less pronounced spontaneous activity in the form of fibrillation potentials and positive sharp waves. Nerve conduction studies in almost all patients reveal evidence of sensory neuronopathy of the axonal type. An electrodiagnostic evidence of motor axonal neuropathy is found in a minority of patients [22, 26, 38]. It is suggested that the electrophysiological phenotype could be linked to CAG expansion length with longer expansions showing a motor-predominant phenotype, while a shorter CAG repetition sequence linked to a sensory-predominant phenotype [39]. Upper and lower extremity somatosensory evoked potentials can be abnormal in the majority of these patients, while only a minority have detectable abnormalities on motor evoked potential studies [26, 40].

Serum CK level is another important testing tool that can further increase the suspicion for KD. Serum CK levels are usually higher than the normal population and patients with other motor disorders but it lacks specificity [41]. Serum creatine level is usually low in the early stages of the disease and may correlate with disease severity [42, 43].

Brain imaging may reveal findings such as reduced volume with atrophy of grey and white matter frontal areas as well as white matter changes in the brainstem and cerebellum. These are typically detected on voxel-based morphometry and diffusion tensor imaging [44, 45]. Neurofilament light chain which is a recognized serum biomarker of neuronal damage has been found to be unchanged in KD compared to ALS patients and does not correlate with clinical progression [46]. Skeletal muscle MRI is an emerging diagnostic tool that could play a future role in differentiating KD from ALS and in evaluating disease progression through quantitative imaging of fat infiltration in muscles [47, 48]. Muscle biopsy is not routinely performed in KD; however, up to this date still a minority of patients may undergo this procedure as part of their workup. As mentioned earlier, muscle pathology exhibit features of both myopathy and denervation [13, 43]. Genetic testing confirming CAG trinucleotide repeat expansion (≥ 38) on the first exon of the androgen receptor remains the gold

standard tool in confirming the diagnosis of KD [4, 5]. Key distinguishing features of different disorders that maybe be mistaken for KD are listed in Table 2.

Management and prognosis

Management of KD starts with disease staging which can be done by measuring disease progression using functional rating scales. The Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS) is a 14-item scale that measures motor function and focus on bulbar related symptoms [49]. KD-1234 scale is another validated ten-item clinical tool used to measure clinical progression [50]. Both scales share similarities with the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-r). The importance of staging disease progression lays in predicting and hopefully preventing the occurrence of complications such as falls, aspirations, and respiratory complications. These can be achieved by the early implementation of canes,

wheelchairs, aspiration precautions and ventilatory support. Up to this date, there is no recognized therapy to halt disease progression. Since KD is caused by a mutation in the androgen receptor, several clinical studies using androgen reducing agents were carried out and unfortunately did not show any clear benefit. Such studies included leuprorelin (leuteinizing hormone-releasing hormone) and dutasteide (5-alpha-reductase inhibitor) [51–53]. A long-term dual arm (treatment–control) small study showed that the use leuprorelin acetate may delay the functional progression of the disease as well as reduce the incidence of pneumonia [54]. A randomized clinical trial using insulin-like growth factor 1 showed a significant difference in thigh muscle volume on MRI compared to placebo group but failed to show significant differences in muscle strength and/or function [55]. A pilot trial of clenbuterol, a β_2 agonist with anabolic effects on skeletal muscles, showed a significant increase in the 6-min walk test and improved functional vital capacity but no change in muscle strength or in the ALSFRS-r score [56]. The safety and efficacy of creatine is currently being

Table 2 Differential diagnosis

Disorder	Distinguishing features
Amyotrophic lateral sclerosis	Rapid progressive course Evidence of upper motor neuron involvement Absence of sensory neuropathy Absence of metabolic manifestations
Primary lateral sclerosis	Evidence of upper motor neuron involvement Absence of axonal polyneuropathy, sensory neuropathy, and metabolic manifestations Abnormal motor evoked potentials
Progressive muscular atrophy	Faster progressive course Absence of axonal polyneuropathy, sensory neuropathy, and metabolic manifestations
Late onset spinal muscular atrophy	Symmetric involvement Proximal > distal weakness pattern Absence of sensory neuropathy Absence of non-neurological manifestations
Distal hereditary motor neuropathy	Early onset Symmetrical involvement Length-dependent pattern Absence of non-neurological manifestations
Chronic inflammatory demyelinating polyneuropathy	Relapsing–remitting course Pronounced sensory polyneuropathy Demyelinating features on neurophysiological testing
Multifocal motor neuropathy	Multiple motor conduction blocks +/- conduction slowing and temporal dispersion No evidence of sensory neuropathy Relatively preserved muscle bulk compared to the degree of weakness
Late onset Tay-Sachs disease (Sandhoff disease)	Presence of cerebellar involvement Psychiatric manifestations Symmetric involvement Abnormal serum hexosaminidase enzyme activity levels No evidence of metabolic abnormalities

tested in a randomized, double blinded, placebo-controlled trial [57]. Physical therapy is recommended for patients with KD similar to patients with other motor neuron disorders, but there is no consensus or scientific data to guide patients and therapists regarding exercise intensity. In a small open label study, the use of regular moderate-intensity cycling exercise failed to show any significant improvement in respiratory functions or in activities of daily living [58]. Another randomized controlled clinical trial failed to show a clear benefit of light-functional exercise on muscle strength, function, balance, or quality of life [59]. However, KD is a gradually progressive disorder with a long-life expectancy whereby patients remain fully ambulatory for the majority of their disease course [24] and the leading cause of death is aspiration pneumonia [23].

Conclusion

In conclusion, KD is an inherited X-linked slowly progressive multisystem disease mainly manifesting with a lower motor neuron disorder phenotype leading to gradual disability. Currently, there are no therapies proven to halt or slow disease progression. Larger long-term population-based studies are needed to better characterize the early manifestations and disease progression. Future preclinical investigations may lead to a better understanding of the underlying pathophysiology that will hopefully lead to the development of disease modifying therapy.

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Compliance with ethical standards

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