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REVIEW

Kennedy's disease (spinal and bulbar muscular atrophy): a clinically oriented review of a rare disease

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Abstract

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare, X-linked hereditary lower motor neuron disease, characterized by progressive muscular weakness. An expanded trinucleotide repeat (CAG > 37) in the androgen receptor gene (AR), encoding glutamine, is the mutation responsible for Kennedy's disease. Toxicity of this mutant protein affects both motor neurons and muscles. In this review, we provide a comprehensive, clinically oriented overview of the current literature regarding Kennedy's disease, highlighting gaps in our knowledge that remain to be addressed in further research. Kennedy's disease mimics are also discussed, as are ongoing and recently completed therapeutic endeavours.

Keywords Kennedy's disease · Spinal and bulbar muscular atrophy · Spinobulbar muscular atrophy · Androgen receptor · X-linked

Introduction

Spinal and bulbar muscular atrophy, also known as Kennedy's disease (SBMA; OMIM 313200), is a rare, X-linked hereditary lower motor neuron disease, characterized by progressive muscular weakness. An expanded trinucleotide repeat (CAG > 37) in the androgen receptor gene (*AR*), encoding glutamine, is the mutation responsible for Kennedy's disease [1]. It is one of the nine neurological disorders caused by a CAG repeat expansion (polyglutamine diseases) and was the first disease where a pathogenic-expanded trinucleotide repeat was identified [2]. Toxicity of the mutant protein affects both motor neurons and muscles.

Although earlier reports exist, particularly in the Japanese literature, description of Kennedy's disease is accredited to William R. Kennedy who described this entity in 11 patients from two different kindred in 1968, noting the sex-linked recessive pattern of inheritance [3]. Harding et al. reclassified Kennedy's disease as X-linked bulbospinal neuronopathy suggesting a sensory neuronopathy in addition to motor neuron loss [4]. In 1986, the causative genetic defect was localized at the *DXYS1* marker, in the X chromosome. In 1991, La Spada et al. [1] identified this genetic defect to be an expanded CAG repeat in the first exon of the AR gene.

In this review, we provide a comprehensive, clinically oriented overview of the current literature regarding Kennedy's disease, highlighting gaps in our knowledge that remain to be addressed in further research.

Methodology

Literature searches were conducted on MEDLINE (PubMed), Scopus, and clinicaltrials.gov, using several key words and their combinations. Search terms included: Kennedy's disease, spinal and bulbar muscular atrophy, spinobulbar muscular atrophy, bulbospinal muscular atrophy, and lower motor neuron disease. References from the selected articles were also thoroughly screened for other pertinent articles. Additional searches were performed for specific topics (e.g., sleep disorders and autonomic dysfunction). During the screening of the abstracts/full texts, the publications that were not relevant to this review were removed. No language or publication period restrictions were applied to the initial

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searches. However, only English-speaking publications were further studied in detail.

Prevalence of SBMA

Kennedy's disease is a very rare disease in most populations. Consequently, prevalence studies of SBMA are uncommon [5]. A recent study from the UK identified only 61 patients over 9 years, despite the creation of a national register for the disease [6]. Nevertheless, previous reports have suggested that SBMA may be underestimated due to limited physician awareness [7], the often quoted prevalence of 1–2 per 100,000 resulting from an underdiagnosis. In fact, Fischbeck reported a prevalence that approaches 1 in 40,000 and Guidetti et al. a prevalence of 1.6/100,000 in Reggio of Italy [8, 9]. Several founder effects are observed, particularly in genetically isolated areas such as the Vasa Region in Western Finland (13/85.000 male inhabitants) [10]. A founder effect also exists in the Japanese population, which explains the fact that Kennedy's disease is much more common in the Japanese than in other ethnic populations [11].

Pathogenesis: mechanism

The exact mechanism by which coding CAG triplet repeat expansion leads to neurodegeneration remains to be elucidated. The common neuropathological feature of all polyglutamine diseases are intranuclear inclusions consisting of misfolded polyglutamine-expanded proteins in affected neuronal populations (Fig. 1).

In SBMA, there is increasing evidence that toxicity of the mutant protein is caused by an androgen-dependent gain of function by the receptor (androgen-dependent neurodegeneration). In normal subjects, the presence of androgen binding by the receptor results in nuclear translocation and regulation of androgen-responsive elements in the genome. In contrast, in Kennedy's disease, the androgen binding by the receptor results in aggregation of the mutant receptor, followed by formation of nuclear inclusions (in tissues where it is expressed), and impairment of its function [12]. Toxicity of the mutant androgen receptor is thus mediated through transcriptional dysregulation and other not well-defined mechanisms [13]. However, a loss-of-function mechanism is also important, explaining the endocrine clinical manifestations of the patients, such as gynecomastia and reduced fertility, in addition to weakness and muscle atrophy.

In affected individuals, degeneration of anterior horn cells in the spinal cord is observed [14]. In addition to neurogenic muscle atrophy, changes in muscle are also noted, with

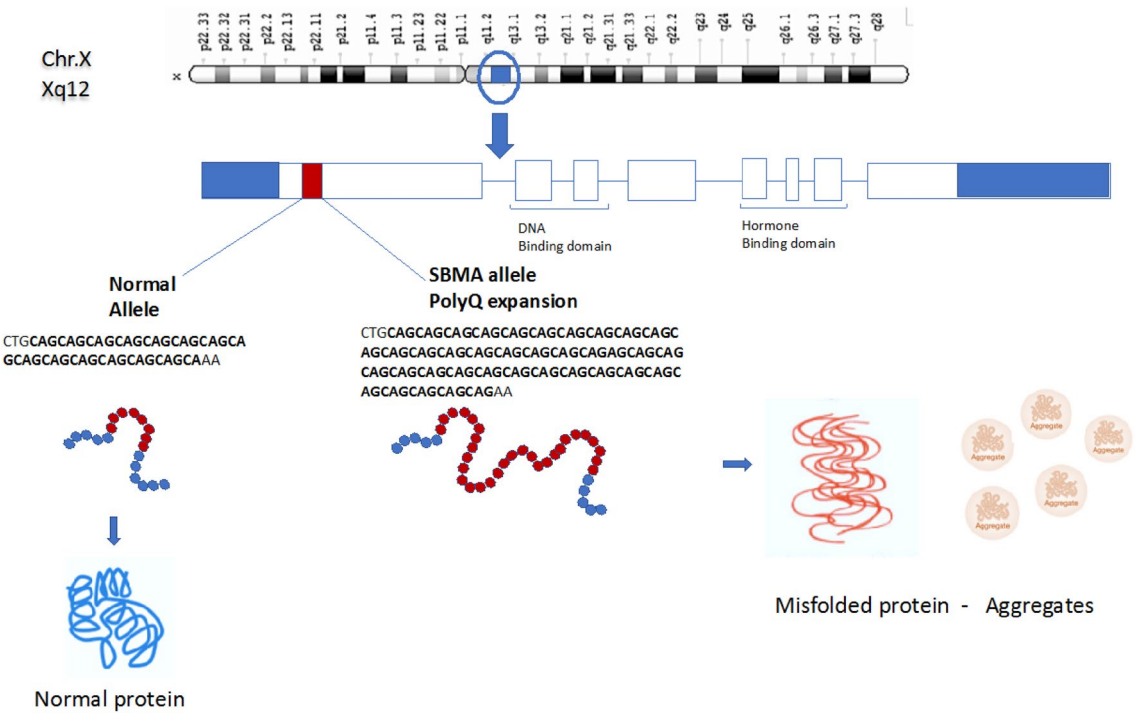

Fig. 1 Schematic diagram showing the pathomechanism of SBMA

evidence of a primary myopathic process, including necrotic myofibers and myofibers with centrally located nuclei [15]. Inclusions of mutated androgen receptor (AR) protein are shown by immunohistochemical methods [16]. The exact mechanism and role of the motor neuron and muscle in the pathogenesis in patients with SBMA are not yet clear [17]. Findings in SBMA mice have partly supported the idea of degeneration of skeletal muscle initially, which resulting in motor neuron dysfunction and loss [18].

Genetic counselling: affected males and females carriers

Asking for family history is important, as patients with Kennedy's disease usually have other affected relatives. SBMA is inherited in an X-linked recessive pattern in contrast to all other polyglutamine diseases that are transmitted in an autosomal-dominant pattern. It affects mainly men. Asymptomatic women usually transmit the disease and only a minority of female carriers (≥ 38 CAG repeats) report mild symptoms such as cramping or tremor [7]. Highly skewed inactivation of the affected X chromosome relates with asymptomatic female carriers of SBMA [19]. In addition, female carriers are protected by their low levels of circulating androgens and, consequently, lower level of androgen receptor stimulation [20].

The absence of X-linked family history does not exclude the diagnosis of Kennedy's disease. Genetic status of the mother determines risk to offspring. The probability of inheriting the pathogenic-expanded CAG trinucleotide expansion for each offspring is 50%, based on the fact that all tested mothers are heterozygotes. Affected males do not transmit the pathogenic CAG trinucleotide expansion to their sons, and all their daughters will be heterozygotes (carriers) [20]. As described in other coding CAG triplet repeat disorders, paternal transmission leads to intergenerational increases in CAG repeat size, indicating that unstable CAG repeats occur during spermatogenesis [21]. This results in the well-described phenomenon of anticipation that is discussed below.

Diagnosis

Diagnosis is established with genetic testing of CAG trinucleotide repeats in the androgen receptor (AR) gene. Expanded repeat lengths of 38–68 CAGs in the *AR* gene are reported in patients with Kennedy's disease [22, 23]. The CAG repeat length range in a normal population is 11–32 CAGs. Interestingly, a contracted CAG repeat in the AR gene was reported in three brothers with mental retardation [24].

An allele of 37 CAG repeats was found in a 46-year-old asymptomatic patient, suggesting that SBMA may manifest as reduced penetrance disease, although follow-up data have not been reported on this case to settle the matter [25]. Given that age at onset of Kennedy's disease is usually estimated between 30 and 50 years and an inverse correlation exists between the age at onset and CAG repeat length, it is expected that such patients could manifest late-onset Kennedy's disease, so late, in fact, that some patients may die before clinical manifestations appear [25]. Consequently, patients with 35–37 CAG repeats should be evaluated periodically over their entire lifespan, in accordance with family history, neurological examination findings, and genotype–phenotype correlations in other family members. Age of onset also inversely correlates with number of CAG triplet repeats in other CAG repeat diseases, such as Huntington's disease [26].

A molecular genetic diagnosis should ideally be established in an affected family member before testing unaffected family members. Sensitivity and specificity of SBMA molecular gene testing are, excepting human error, 100%, and it is available in clinical reference laboratories worldwide.

Laboratory testing of serum creatine kinase (CK) and electrophysiology studies are frequently abnormal at the time of diagnosis. Creatine kinase (CK) level is usually elevated, in about 80% of SBMA patients (> 3–4 times), and it may precede other symptoms [27]. Liver enzymes are also often elevated, and metabolic disturbances such as diabetes, dyslipidaemia, and hypercholesterolemia are noted [28–30]. A recent study has demonstrated that serum creatinine levels begin to decrease before symptom onset, suggesting that they may be a useful biomarker for preclinical SBMA progression [31].

Differential diagnosis: Kennedy's disease mimics

Time to SBMA diagnosis after onset of weakness averaged 5.5 years, and the time from first medical evaluation to diagnosis averaged more than 3 years [32]. This could be attributed to the fact that many patients with Kennedy's disease are misdiagnosed in the beginning as having amyotrophic lateral sclerosis (ALS), as there are a lot of common symptoms and signs between SBMA and other motor neuron diseases. Parboosingh et al. reported that 2% of patients diagnosed with ALS actually suffer from Kennedy's disease [33]. Unlike SBMA, disease progression in ALS is significantly more rapid. Moreover, androgen insensitivity is not observed in ALS. On examination, individuals with ALS have upper motor neuron signs, such as hyperreflexia and spasticity, and greater asymmetry is noted. However, early on in the

disease, these may not be evident. In comparison to ALS, lower sensory nerve action potential (SNAP) amplitudes are seen in Kennedy's disease, providing another useful tool in the differential diagnosis of these two diseases [34].

Hereditary causes that can mimic SBMA include spinal muscular atrophy (SMA) type IV and distal hereditary motor neuropathies (dHMNs) [35]. An overlap of symptomatology also exists between SBMA disease and other diseases such as metabolic myopathies, myasthenia gravis, and polymyositis [36]. Other non-hereditary Kennedy's disease mimics include progressive muscular atrophy (PMA), infections (post-polio syndrome), structural lesions (spinal cord arteriovenous malformations), paraneoplastic syndromes, and toxins (chronic lead poisoning) [20].

Atypical SBMA cases may often lead to misdiagnosis. Unusual clinical presentations such as jaw drop, myotonia-like symptoms, and pure symptomatic bulbar phenotype have been rarely reported, expanding the known phenotype associated with SBMA [37–39]. In addition, a 29-year-old patient with SBMA with a 68 CAG repeat expansion in the AR gene, the largest repeat CAG size that has been reported so far, presented with atypical manifestations [23]. This patient had the early onset of disease at age 18, autonomic dysfunction, and abnormal sexual development.

Clinical phenomenology

Muscle weakness and wasting of the limbs, bulbar weakness, tremor, cramps, fasciculations, sensory neuropathy, gynecomastia, and sexual dysfunction are the major clinical manifestations of Kennedy's disease (Table 1) [3, 40]. Intra-familial variability in clinical features of the disease has been reported [41].

Motor manifestations

As SBMA is a lower motor neuron disease, muscle weakness is the main clinical motor manifestation. The most common presenting symptom that brings patients to the hospital is lower limb weakness (90%) [6, 22]. However, other symptoms such as cramps or tremor may precede the onset of muscle weakness. We should note that early in the disease course, muscle weakness in the lower limbs is usually more proximal than distal, which could serve as a clinical hint in differential diagnosis with dHMN. Tremor is usually a high-frequency postural tremor of the hands. Postural leg tremor has also been described in some SBMA patients [42]. On examination, muscle atrophy, fasciculations, decreased, or absent tendon reflexes are observed. Bulbar muscle weakness is rarely the presenting symptom. Usually, it follows lower limb weakness and manifests as fasciculations of the tongue with midline furrowing due to wasting of glossal muscles (Fig. 2, video-supplementary file), fasciculations–myokymia of perioral region, dysarthria, and dysphagia [43, 44]. In almost 80% of SBMA patients, dysphagia is found, particularly during the later course of the disease [43]. Laryngospasms are noted in some patients [45]. Twitching movements of the chin (perioral fasciculations-myokymia), known as "quivering chin", may appear due to spontaneous motor unit discharges or voluntary contractions of the perioral muscles [46]. Perioral fasciculations are also an important clinical hint to the diagnosis of Kennedy's disease, especially if associated with other characteristics of Kennedy's

Table 1 Cardinal clinical features and other instrumental findings in Kennedy's disease

Cardinal clinical features	Other instrumental findings
Neurological	
Lower limb muscle weakness and atrophy	Elevated CPK
Upper limb muscle weakness and atrophy	Hyperlipidemia
Bulbar muscle weakness (dysarthria and dysphagia)	Diabetes
Fasciculations (tongue and diffuse muscle fasciculations and perioral myokymia-quivering chin)	Non-alcoholic fatty liver disease
Tremor	EMG/NCS: acute and chronic diffuse denervation atrophy, (anterior horn cell loss), and low SNAP amplitudes (sensory neuropathy)
Cramps	
Decreased or absent tendon reflexes	
Sensory symptoms (numbness and tingling)	
Non-neurological	
Gynecomastia	
Testicular atrophy	
Reduced fertility	
Erectile dysfunction	

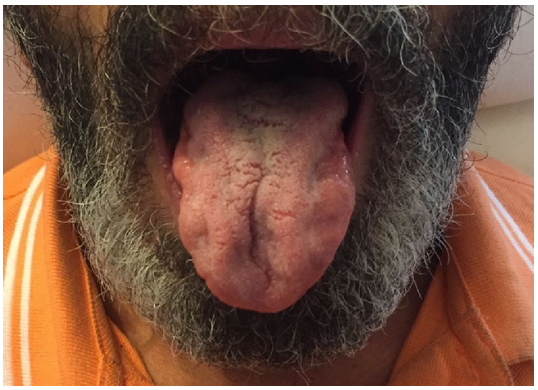

Fig. 2 61-year-old SBMA patient with wasting of the tongue, scalloping of the borders, and midline furrowing

disease like proximal muscle atrophy and gynecomastia [47]. Respiratory failure is uncommon, even in advanced stages of the disease. However, any indications or respiratory distress should prompt further respiratory testing.

Non-motor manifestations

Sensory symptoms, like numbing and tingling, are also reported mainly in the distal limbs, in more than half of SBMA patients, but usually in later course of the disease [48]. Although autonomic nervous system involvement is not considered as part of Kennedy's disease, evidence exists that the autonomic nervous system may be subclinically involved [49].

While the neurological features of SBMA patients are well known, the non-neural clinical involvement has been less extensively investigated. Signs of androgen insensitivity, such as gynecomastia, reduced fertility, and testicular atrophy, are observed in SBMA affected males, sometimes beginning in adolescence and continuing through adulthood [36]. SBMA patients may experience problems such as low-sperm count and erectile dysfunction.

Regarding sleep abnormalities in SBMA, obstructive sleep apnea (OSA) is the most common sleep disorder [50]. Sleep quality is poorer in Kennedy's disease patients in comparison to controls. It is noteworthy that, in a recent study, 22% of SBMA patients showed periodic limb movements in sleep [50].

Cardiological investigations indicate a Brugada-like electrocardiogram, with a coved or saddle-back-type ST-segment elevation in more than one right precordial lead, in about 12% of patients in a Japanese study [51]. A downregulation of the *SCN5A* is thought to be the causative effect, leading to sodium reduction in the myocardium [51]. No signs of structural cardiomyopathy are reported in this study, but it is noteworthy that a symptomatic Brugada syndrome was recorded in two patients, who died abruptly. Interestingly, an Italian study confirmed Brugada ECG abnormalities in three SBMA patients (4%), albeit at a lower percentage [29]. However, Brugada syndrome is known to be more frequent in the Asian than the European population. These findings highlight the need for ECG testing in SBMA patients. More specifically, to enhance sensitivity for the detection of Brugada-like ECG changes, the recommendation is to record in non-conventional upward right precordial leads, V1–V2 over the III and II intercostal space. Patients presenting with these abnormal findings in ECG should be monitored closely by a cardiologist, avoid high fever, hypokalemia, and use antiarrhythmic drugs with caution [51]. Further studies are needed to evaluate ECG changes in SBMA in other populations.

Metabolic disturbances are also reported In Kennedy's syndrome. Total cholesterol, LDL, and triglycerides are usually elevated, and diabetes often coexists in SBMA patients in several studies, implying the existence of a partial metabolic syndrome in these patients [6, 22, 29, 32, 52]. Non-alcoholic fatty liver disease is observed in a recent study [53]. The underlying mechanism is unknown and therapeutic dilemmas exist regarding the use of statins in SBMA patients. Statin-associated muscle toxicity is a well-known adverse event of statins, raising safety issues when considering statins as treatment in SBMA patients [29].

In a recent study, more than 40% of patients with SBMA reported moderate or severe lower urinary tract symptoms (LUTS) in the absence of benign prostatic hyperplasia [29]. The exact mechanism responsible for bladder obstruction is not yet clear. Androgen sensitivity is postulated, since low androgen levels have been associated with a higher risk of bladder outlet obstruction [29].

Central nervous system involvement has also been described in SBMA patients. Recent studies highlight decrease in grey matter volume, particularly in frontal areas. White matter atrophy is also reported [54]. These findings are in agreement with clinical aspects of SBMA phenotype, such as behavioural abnormalities, and with histopathology of the disease [55, 56]. In addition, glucose hypometabolism in frontal areas was found in a study of ten SBMA patients who underwent PET studies [57]. Results of all relevant studies suggest a subclinical involvement of the upper motor neuron in Kennedy's disease.

Age of onset

Age of onset is usually estimated between 35 and 40 years [28]. However, there are a few cases reporting onset before adulthood [58]. Age of onset and symptoms at onset are still under debate, due to the high variability between studies. Manifestations such as gynecomastia, testicular atrophy, and tremor may precede, by years, the onset of muscular weakness, appearing even in adolescence. Unreliable information

regarding the initial manifestations of SBMA may lead to an erroneous age of onset of SBMA. This could be attributed to the fact that manifestations like tremor or cramps are often not recognized as onset manifestations. Only motor symptoms are usually reported as onset symptoms of SBMA. Furthermore, SBMA patients may not be fully aware of symptoms such as easy fatigability, tremor, or cramps, and, thus, may not be able to pinpoint the exact age of onset of each symptom [7]. Nevertheless, non-motor manifestations should also be recognized as onset manifestations [40].

Genotype–phenotype correlations

An inverse correlation exists between the number of CAG repeats and age of disease onset, as assessed by muscle weakness [1, 59]. In addition, earlier age of disease onset correlates with reaching individual activity daily living (ADL) milestones earlier (handrail, cane, wheelchair-bound, death), as it is described in those with longer CAG repeats [22]. Consequently, SBMA males with a larger number of CAG repeats tend to have earlier disease onset and reach disability milestones earlier [59]. Bulbar symptoms, gynecomastia, and insulin resistance also correlate with the length of the CAG repeat [22, 60]. However, progression rate (defined as rate of decline between milestones) is not correlated with CAG repeat size [22].

Only 60% of the variability observed could be attributed to CAG repeat number, indicating that other factors such as environmental effects, and genetic and epigenetic modifiers exist [20]. The fact that relatives with SBMA and an identical CAG repeat number may have different disease course further supports this statement.

Electrodiagnostic studies and muscle biopsy

Over 90% of patients with Kennedy's disease will have abnormal nerve conduction studies [28]. Symptomatic female carriers with cramps or tremor may also have abnormal electromyography [34, 61]. Diffuse denervation atrophy, anterior horn cell loss, and sensory neuropathy are common findings in electrodiagnostic testing of SBMA patients. Low SNAP amplitudes are observed. A significant proportion though is reported to have normal SNAPs [10]. Small myelinated and unmyelinated fibers are also involved, as shown in a skin biopsy study, which could explain the neuropathic pain reported by some SBMA patients [62]. Furthermore, a neurophysiological study of trigeminal reflexes indicated a trigeminal ganglionopathy [63]. Myopathic changes, such as central nuclei and myofibrillar disorganization, have been noted in addition to neurogenic changes (fiber-type grouping, angulated fibers) in muscle biopsy [64]. Regarding the quivering chin, grouped repetitive discharges suggestive of myokymia have been recorded, although there is some controversy around whether they constitute true myokymia rather than fasciculations [48, 65].

Prognosis and management of Kennedy's disease

A slow disease progression in Kennedy's disease patients is described, with good mobility preservation until the late stages of disease [13]. The use of a wheelchair starts at a median age of about 60 years [22]. Even in the early stages of the disease, SBMA patients can present with manifestations such as dysarthria, which may progress to dysphagia. Life expectancy of these patients, however, is not significantly affected [40]. SBMA patients usually have a normal life expectancy, although there is a higher risk of choking and aspiration pneumonia because of bulbar weakness [22]. In comparison to other motor neuron diseases (e.g., ALS), disease progression is slow, with muscle strength declining only by 2% per year [66].

Currently, no disease-modifying treatment is established for SBMA. As a result, management of SBMA is focused on preventing complications of the disease, such as falls, fractures, aspiration, and reduced mobility. While dyspnoea is unusual, shortness of breath should be investigated with pulmonary function testing. A swallowing study should be performed in patients with dysphagia to exclude aspiration risk. Video fluorography with barium is used to assess such deficits in swallowing [44]. Specific exercises adjusted to the functional level of each patient and prophylactic measures are advised to reduce the risk of aspiration and enhance mobility of SBMA patients. However, the exact role of exercise is not yet clear and there was no significant effect from different studies [67].

Clinical trials and ongoing studies

The therapeutic target of most clinical trials in SBMA is to reduce the AR ligand. To date, most trials have failed to demonstrate a clear therapeutic benefit, paving the way for a promising intervention in SBMA.

Leuprorelin is a hormone analogue that reduces the production of testosterone and, consequently, dihydrotestosterone. It was shown to decrease disease manifestations in transgenic mouse models of SBMA [68]. Subsequent studies on patients with SBMA did not show a significant improvement compared with placebo in the ALS Functional Rating Scale (ALSFR) [69, 70]. However, a recent long-term study concluded that treatment with leuprorelin acetate appears to delay the functional decline

and suppress the incidence of pneumonia and death in SBMA patients [70]. Dutasteride, is another agent, a 5a-reductase inhibitor, which was evaluated in a 2-year randomized, double-blind, placebo-controlled study of 50 SBMA patients and found to have no effect on the primary measure of muscle strength [66]. Clenbuterol is a β2-adrenoceptor agonist usually used in asthma, as it has an anabolic effect, increasing skeletal muscle mass and decreasing body fat. Therefore, a pilot trial was conducted to test efficacy and tolerability of clenbuterol in 16 SBMA patients, showing an increase in the 6-min walk test and forced vital capacity after 12 months [71]. Further randomized placebo-controlled studies of drugs in this class are needed to investigate functional efficacy. Recently, a RNA interference strategy to target AR for suppression was studied, achieving reduction of polyglutamine-expanded AR expression in a mouse model of SBMA using miRNAs targeting AR [72].

Clinicaltrials.gov was searched for ongoing studies. Presently, three ongoing studies investigating patients with SBMA were noted. (1) NCT02124057 is an observational study of hepatic function in patients with SBMA. Preliminary data in SBMA patients indicated increased hepatic fat. This study has been recently published, reporting the evidence of non-alcoholic liver disease in nearly all of the participants with SBMA, expanding the phenotypic spectrum of the disease and providing a potential biomarker for future studies [53]. (2) NCT02501395—MRI in patients with Kennedy's disease—is an observational case–control study which aims to investigate the muscle involvement in patients with Kennedy's disease using MRI. (3) NCT02156141—High Intensity Training in patients with SBMA (HIT in Kennedy)—is an interventional clinical trial, investigating if high intensity training can increase daily functionality without causing muscle damage in patients with SBMA.

Current status and future prospects

Kennedy's disease is a rare disease. There is an urgent need to obtain data in rare diseases from different populations with variable genetic backgrounds so as to confirm phenotypic homogeneity and obtain sufficient power for future clinical trials. This could be achieved by connecting different SBMA clinics and creating a network of international collaborations, an international SBMA registry [73]. In this context, a European neuromuscular workshop on SBMA took place in March 2015, and an agreement was made between several SBMA centres to use a common protocol for SBMA patients, to build an international SBMA registry [74].

Conclusions

SBMA is not just a lower motor neuron disease but a complex disorder affecting different systems, including the central nervous system. Insights on the expanding phenotypic spectrum of Kennedy's disease may unravel the pathogenic mechanisms of the disease and identify novel biomarker candidates, contributing towards future therapeutic interventions.

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Compliance with ethical standards

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References

1. La Spada AR, Wilson EM, Lubahn DB et al (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 352:77–79. https://doi.org/10.1038/352077a0
2. Pennuto M, Rinaldi C (2017) From gene to therapy in spinal and bulbar muscular atrophy: are we there yet? Mol Cell Endocrinol. https://doi.org/10.1016/j.mce.2017.07.005
3. Kennedy WR, Alter M, Sung JH (1968) Progressive proximal spinal and bulbar muscular atrophy of late onset. Neurology 18
4. Harding AE, Thomas PK, Baraitser M et al (1982) X-linked recessive bulbospinal neuronopathy: a report of ten cases. J Neurol Neurosurg Psychiatry 45:1012–1019. https://doi.org/10.1136/jnnp.45.11.1012
5. Koutsis G, Kladi A, Breza M et al (2015) Spinobulbar muscular atrophy (Kennedy's disease): a rare diagnosis in the Greek population. J Neurol Sci 359:450–451. https://doi.org/10.1016/j.jns.2015.10.021
6. Fratta P, Nirmalananthan N, Masset L et al (2014) Correlation of clinical and molecular features in spinal bulbar muscular atrophy. Neurology 82:2077–2084. https://doi.org/10.1212/WNL.0000000000000507
7. Mariotti C, Castellotti B, Pareyson D et al (2000) 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. Neuromuscul Disord 10:391–397. https://doi.org/10.1016/S0960-8966(99)00132-7
8. Fischbeck KH (1997) Kennedy disease. J Inherit Metab Dis 20:152–158. https://doi.org/10.1023/A:1005344403603
9. Guidetti D, Sabadini R, Ferlini A, Torrente I (2001) Epidemiological survey of X-linked bulbar and spinal muscular atrophy, or Kennedy disease, in the province of Reggio Emilia, Italy. Eur J Epidemiol 17:587–591. https://doi.org/10.1023/A:1014580219761

10. Udd B, Juvonen V, Hakamies L et al (1998) High prevalence of Kennedy's disease in Western Finland—is the syndrome underdiagnosed? Acta Neurol Scand 98:128–133
11. Tanaka F, Doyu M, Ito Y et al (1996) Founder effect in spinal and bulbar muscular atrophy (SBMA). Hum Mol Genet 5:1253–1257. https://doi.org/10.1093/hmg/5.9.1253
12. Li M, Miwa S, Kobayashi Y et al (1998) Nuclear inclusions of the androgen receptor protein in spinal and bulbar muscular atrophy. Ann Neurol 44:249–254. https://doi.org/10.1002/ana.410440216
13. Grunseich C, Fischbeck KH (2015) Spinal and bulbar muscular atrophy. Neurol Clin 33:847–854. https://doi.org/10.1016/j.ncl.2015.07.002
14. Amato A, Prior TW, Barohn RJ et al (1993) Kennedy's disease: a clinicopathologic correlation with mutations in the androgen receptor gene. Neurology 43:791–794
15. Cortes CJ, Ling SC, Guo LT et al (2014) Muscle expression of mutant androgen receptor accounts for systemic and motor neuron disease phenotypes in spinal and bulbar muscular atrophy. Neuron 82:295–307. https://doi.org/10.1016/j.neuron.2014.03.001
16. Adachi H, Katsuno M, Minamiyama M et al (2005) Widespread nuclear and cytoplasmic accumulation of mutant androgen receptor in SBMA patients. Brain 128:659–670. https://doi.org/10.1093/brain/awh381
17. Rinaldi C, Bott LC, Fischbeck KH (2014) Muscle matters in Kennedy's disease. Neuron 82:251–253. https://doi.org/10.1016/j.neuron.2014.04.005
18. Rocchi A, Milioto C, Parodi S et al (2016) Glycolytic to oxidative fiber type switch and mTOR signaling activation are early-onset features of SBMA muscle modified by high fat diet. Acta Neuropathol 132:127–144. https://doi.org/10.1007/s00401-016-1550-4
19. Ishihara H, Kanda F, Nishio H et al (2001) Clinical features and skewed X-chromosome inactivation in female carriers of X-linked recessive spinal and bulbar muscular atrophy. J Neurol 248:856–860. https://doi.org/10.1007/s004150170069
20. La Spada A (1996) Spinal and bulbar muscular atrophy. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A (eds) GeneReviews®. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1333/. Accessed 10 mar 2018
21. Biancalana V, Serville F, Pommier J et al (1992) Moderate instability of the trinucleotide repeat in spinobulbar muscular atrophy. Hum Mol Genet 1:255–258
22. Atsuta N, Watanabe H, Ito M et al (2006) Natural history of spinal and bulbar muscular atrophy (SBMA): a study of 223 Japanese patients. Brain 129:1446–1455. https://doi.org/10.1093/brain/awl096
23. Grunseich C, Kats IR, Bott LC et al (2014) Early onset and novel features in a spinal and bulbar muscular atrophy patient with a 68 CAG repeat. Neuromuscul Disord 24:978–981. https://doi.org/10.1016/j.nmd.2014.06.441
24. Kooy RF, Reyniers E, Storm K et al (1999) CAG Repeat contraction in the androgen receptor gene in three brothers with mental retardation. Am J Med Genet 213:209–213
25. Kuhlenbäumer G, Kress W, Ringelstein EB, Stögbauer F (2001) Thirty-seven CAG repeats in the androgen receptor gene in two healthy individuals. J Neurol 248:23–26. https://doi.org/10.1007/s004150170265
26. Koutsis G, Karadima G, Kladi A, Panas M (2014) Late-onset Huntington's disease: diagnostic and prognostic considerations. Parkinsonism Relat Disord 20:726–730. https://doi.org/10.1016/j.parkreldis.2014.03.017
27. Chahin N, Sorenson EJ (2009) Serum creatine kinase levels in spinobulbar muscular atrophy and amyotrophic lateral sclerosis. Muscle Nerve 40:126–129. https://doi.org/10.1002/mus.21310
28. Rhodes LE, Freeman BK, Auh S et al (2009) Clinical features of spinal and bulbar muscular atrophy. Brain 132:3242–3251. https://doi.org/10.1093/brain/awp258
29. Querin G, Bertolin C, Da Re E et al (2015) Non-neural phenotype of spinal and bulbar muscular atrophy: results from a large cohort of Italian patients. J Neurol Neurosurg Psychiatry. https://doi.org/10.1136/jnnp-2015-311305
30. Manzano R, Sorarú G, Grunseich C et al (2018) Beyond motor neurons: expanding the clinical spectrum in Kennedy' s disease. J Neurol Neurosurg Psychiatry. https://doi.org/10.1136/jnnp-2017-316961
31. Hijikata Y, Hashizume A, Yamada S et al (2018) Biomarker-based analysis of preclinical progression in spinal and bulbar muscular atrophy. Neurology. https://doi.org/10.1212/WNL.0000000000005360.
32. Rhodes LE, Freeman BK, Auh S et al (2009) Clinical features of spinal and bulbar muscular atrophy. Brain 25:285–287. https://doi.org/10.1093/brain/awp258
33. Parboosingh JS, Figlewicz D, Krizus A et al (1997) Spinobulbar muscular atrophy can mimic ALS: the importance of genetic testing in male patients with atypical ALS. Neurology 49:568–572. https://doi.org/10.1212/WNL.49.2.568
34. Ferrante M, Wilbourn AJ (1997) The characteristic electrodiagnostic features of Kennedy's disease. Muscle Nerve 20:323–329
35. Garg N, Park SB, Vucic S et al (2016) Differentiating lower motor neuron syndromes. J Neurol Neurosurg Psychiatry. https://doi.org/10.1136/jnnp-2016-313526
36. Fischbeck KH (2016) Spinal and Bulbar Muscular Atrophy. J Mol Neurosci 58:317. https://doi.org/10.1007/s12031-015-0674-7
37. Sumner CJ, Fischbeck KH (2002) Jaw drop in Kennedy's disease. Neurology 59:1471–1472. https://doi.org/10.1212/01.WNL.0000033325.01878.13
38. Praline J, Guennoc AM, Malinge MC et al (2008) Pure bulbar motor neuron involvement linked to an abnormal CAG repeat expansion in the androgen receptor gene. Amyotroph Lateral Scler 9:40–42. https://doi.org/10.1080/17482960701553915
39. Araki K, Nakanishi H, Nakamura T et al (2015) Myotonia-like symptoms in a patient with spinal and bulbar muscular atrophy. Neuromuscul Disord 25:913–915. https://doi.org/10.1016/j.nmd.2015.08.006
40. Finsterer J, Soraru G (2015) Onset manifestations of spinal and bulbar muscular atrophy (Kennedy's disease). J Mol Neurosci. https://doi.org/10.1007/s12031-015-0663-x
41. Finsterer J (2009) Bulbar and spinal muscular atrophy (Kennedy's disease): a review. Eur J Neurol 16:556–561. https://doi.org/10.1111/j.1468-1331.2009.02591.x
42. Nishiyama A, Sugeno N, Tateyama M et al (2014) Postural leg tremor in X-linked spinal and bulbar muscular atrophy. J Clin Neurosci 21:799–802. https://doi.org/10.1016/j.jocn.2013.07.026
43. Warnecke T, Oelenberg S, Teismann I et al (2009) Dysphagia in X-linked bulbospinal muscular atrophy (Kennedy disease). Neuromuscul Disord 19:704–708. https://doi.org/10.1016/j.nmd.2009.06.371
44. Hashizume A, Banno H, Katsuno M et al (2017) Quantitative assessment of swallowing dysfunction in patients with spinal and bulbar muscular atrophy. Intern Med 56:3159–3165. https://doi.org/10.2169/internalmedicine.8799-16
45. Sperfeld AD, Hanemann CO, Ludolph AC, Kassubek J (2005) Laryngospasm: an underdiagnosed symptom of X-linked spinobulbar muscular atrophy. Neurology 64:753–754. https://doi.org/10.1212/01.WNL.0000151978.74467.E7
46. Finsterer J (2010) Perspectives of Kennedy's disease. J Neurol Sci 298:1–10. https://doi.org/10.1016/j.jns.2010.08.025
47. Pedroso JL, Vale TC, Barsottini OG et al (2018) Perioral and tongue fasciculations in Kennedy's disease. Neurol Sci 39:777–779. https://doi.org/10.1007/s10072-017-3170-8

48. Jokela ME, Udd B (2015) Diagnostic clinical, electrodiagnostic and muscle pathology features of spinal and bulbar muscular atrophy. J Mol Neurosci. https://doi.org/10.1007/s12031-015-0684-5
49. Rocchi C, Greco V, Urbani A, Giorgio A (2011) Subclinical autonomic dysfunction in spinobulbar muscular atrophy. Muscle Nerve 44:737–740. https://doi.org/10.1002/mus.22159
50. Romigi A, Liguori C, Placidi F et al (2014) Sleep disorders in spinal and bulbar muscular atrophy (Kennedy's disease): a controlled polysomnographic and self-reported questionnaires study. J Neurol 261:889–893. https://doi.org/10.1007/s00415-014-7293-z
51. Araki A, Katsuno M, Suzuki K et al (2014) Brugada syndrome in spinal and bulbar muscular atrophy. Neurology 82:1813–1821. https://doi.org/10.1212/WNL.0000000000000434
52. Rosenbohm A, Hirsch S, Volk AE et al (2018) The metabolic and endocrine characteristics in spinal and bulbar muscular atrophy. J Neurol 265:1–11. https://doi.org/10.1007/s00415-018-8790-2
53. Guber RD, Takyar V, Kokkinis A et al (2017) Nonalcoholic fatty liver disease in spinal and bulbar muscular atrophy. Neurology 89:2481–2490. https://doi.org/10.1212/WNL.0000000000004748
54. Kassubek J, Juengling FD, Sperfeld A (2007) Widespread white matter changes in Kennedy disease: a voxel based morphometry study. J Neurol Neurosurg Psychiatry 78:1209–1213. https://doi.org/10.1136/jnnp.2006.112532
55. Soukup GR, Sperfeld AD, Uttner I et al (2009) Frontotemporal cognitive function in X-linked spinal and bulbar muscular atrophy (SBMA): a controlled neuropsychological study of 20 patients. J Neurol 256:1869–1875. https://doi.org/10.1007/s00415-009-5212-5
56. Di Rosa E, Sorarù G, Kleinbub JR et al (2014) Theory of mind, empathy and neuropsychological functioning in X-linked Spinal and Bulbar Muscular Atrophy: a controlled study of 20 patients. J Neurol 262:394–401. https://doi.org/10.1007/s00415-014-7567-5
57. Lai TH, Liu RS, Yang BH et al (2013) Cerebral involvement in spinal and bulbar muscular atrophy (Kennedy's disease): a pilot study of PET. J Neurol Sci 335:139–144. https://doi.org/10.1016/j.jns.2013.09.016
58. Sperfeld AD, Karitzky J, Brummer D et al (2002) X-linked bulbospinal neuronopathy. Arch Neurol 59:1921. https://doi.org/10.1001/archneur.59.12.1921
59. Igarashi S, Tanno Y, Onodera O et al (1992) Strong correlation between the number of CAG repeats in androgen receptor genes and the clinical onset of features of spinal and bulbar muscular atrophy. Neurology 42:2300–2302
60. Nakatsuji H, Araki A, Hashizume A et al (2017) Correlation of insulin resistance and motor function in spinal and bulbar muscular atrophy. J Neurol 264:839–847. https://doi.org/10.1007/s00415-017-8405-3
61. Sobue G, Doyu M, Kachi T et al (1993) Subclinical phenotypic expressions in heterozygous females of X-linked recessive bulbospinal neuronopathy. J Neurol Sci 117:74–78. https://doi.org/10.1016/0022-510X(93)90157-T
62. Manganelli F, Iodice V, Provitera V et al (2007) Small-fiber involvement in spinobulbar muscular atrophy (Kennedy's disease). Muscle Nerve 36:816–820. https://doi.org/10.1002/mus.20872
63. Antonini G, Gragnani F, Romaniello A et al (2000) Sensory involvement in spinal-bulbar muscular atrophy (Kennedy's disease). Muscle Nerve 23:252–258
64. Banno H (2012) Molecular pathophysiology and disease-modifying therapies for spinal and bulbar muscular atrophy. Arch Neurol 69:436. https://doi.org/10.1001/archneurol.2011.2308
65. Meriggioli MN, Rowin J, Sanders DB (1999) Distinguishing clinical and electrodiagnostic features of X-linked bulbospinal neuronopathy. Muscle Nerve 22:1693–1697
66. Fernández-Rhodes LE, Kokkinis AD, White MJ et al (2011) Efficacy and safety of dutasteride in patients with spinal and bulbar muscular atrophy: a randomised placebo-controlled trial. Lancet Neurol 10:140–147. https://doi.org/10.1016/S1474-4422(10)70321-5
67. Dahlqvist JR, Vissing J (2016) Exercise therapy in spinobulbar muscular atrophy and other neuromuscular disorders. J Mol Neurosci 58:388–393. https://doi.org/10.1007/s12031-015-0686-3
68. Katsuno M, Adachi H, Doyu M et al (2003) Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy. Nat Med 9:768–773. https://doi.org/10.1038/nm878
69. Banno H, Katsuno M, Suzuki K et al (2009) Phase 2 trial of leuprorelin in patients with spinal and bulbar muscular atrophy. Ann Neurol 65:140–150. https://doi.org/10.1002/ana.21540
70. Hashizume A, Katsuno M, Suzuki K et al (2017) Long-term treatment with leuprorelin for spinal and bulbar muscular atrophy: Natural history-controlled study. J Neurol Neurosurg Psychiatry 88:1026–1032. https://doi.org/10.1136/jnnp-2017-316015
71. Querin G, D'Ascenzo C, Peterle E et al (2013) Pilot trial of clenbuterol in spinal and bulbar muscular atrophy. Neurology 80:2095–2098. https://doi.org/10.1212/WNL.0b013e318295d766
72. Pourshafie N, Lee PR, Chen K et al (2016) MiR-298 counteracts mutant androgen receptor toxicity in spinal and bulbar muscular atrophy. Mol Ther. https://doi.org/10.1038/mt.2016.13
73. Weydt P, Sagnelli A, Rosenbohm A et al (2015) Clinical trials in spinal and bulbar muscular atrophy—past, present, and future. J Mol Neurosci. https://doi.org/10.1007/s12031-015-0682-7
74. Pareyson D, Fratta P, Pradat P et al (2016) Towards a european registry and biorepository for patients with spinal and bulbar muscular atrophy. J Mol Neurosci. https://doi.org/10.1007/s12031-015-0704-5