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Kennedy's Disease – Current State Of Knowledge

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Abstract

Introduction: Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare X-linked neuromuscular disorder primarily affecting lower motor neuron. It is caused by a CAG trinucleotide repeat expansion in the androgen receptor gene. SBMA typically presents with late-onset, slowly progressive muscle weakness and atrophy, involving both bulbar and extremity muscles. Diagnosis

is frequently delayed, particularly in individuals without a known family history of the disease, with an average diagnostic lag of approximately five years.

Purpose: This paper aims to analyze and synthesize the current state of knowledge on SBMA spanning early clinical presentation, diagnostic processes, management of multifaceted symptoms, and emerging therapeutic strategies.

Methodology: The PubMed and Google Scholar database were searched for scientific articles published between 2015-2024 where 'Spinal and bulbar muscular atrophy', 'Kennedys disease' appears as keywords.

Conclusion: SBMA clinically presents with progressive muscle weakness, bulbar dysfunction, tremor, and metabolic disturbances, often beginning between the ages of 30 and 50. Many patients experience a prolonged and convoluted diagnostic pathway, often involving misdiagnosis and unnecessary or invasive interventions. While no curative treatment currently exists, management focuses on supportive multidisciplinary care, including physical therapy, neurologopedic intervention, and nutritional and respiratory monitoring. Experimental therapies targeting the androgen receptor pathway and molecular mechanisms are under investigation, offering hope for future disease-modifying strategies. Continued research and individualized care remain essential to improving outcomes and quality of life in patients with SBMA.

Keywords: Spinal and bulbar muscular atrophy, Kennedy's disease

Introduction

SBMA, also known as Kennedy's disease, is a rare X-linked neuromuscular disorder that primarily affectis lower motor neuron caused by a CAG trinucleotide repeat expansion in the androgen receptor gene. It has an estimated prevalence of approximately 1 in 40,000 males. Regional variations exist, with notably higher prevalence observed in specific areas such as the Vaasa district in Finland [1]. Despite these figures, comprehensive epidemiological data remain scarce. SBMA represents an important clinical challenge due to its multisystem involvement, diagnostic delay,

and impact on quality of life. Greater awareness and understanding of this condition are essential for timely diagnosis, appropriate management, and improved patient outcomes.

In this study we describe SBMA clinical presentation, diagnostic processes, management of multifaceted symptoms, and emerging therapeutic strategies.

Objective

The aim of this review is to analyze and summarize the current state of knowledge on SBMA- with the goal of fostering earlier recognition and improving outcomes for affected individuals.

Methodology

The PubMed and Google Scholar database were searched for scientific articles published between 2015-2024 although older publications were cited in cases where current evidence was insufficient. Publications were chosen by the year of publication and presence of keywords such as ‘Spinal and bulbar muscular atrophy’, ‘Kennedys disease’ obtaining 4 490 results – PubMed (190) Google Scholar (4300).

Results:

Pathophysiology

Androgen receptor (AR), is a nuclear receptor belonging to the steroid hormone receptor family. The presence of androgen binding by the receptor results in nuclear translocation and regulation of androgen-responsive elements in the genome. [2] Thus Heterozygous females do not display fulminant motor neuron disease because of their low levels of circulating testosterone, thereby preventing nuclear entry of mutated AR protein [3].

The root cause of SBMA is the expansion of a trinucleotide CAG repeat within the first exon of the AR gene located on chromosome X, leading to a stretch of glutamines (a polyglutamine tract) in the AR protein [4]. Expansions of more than 38 CAG trinucleotide repeats lead to the production of a pathological protein known as

polyQ-AR. As a result, KD is classified among the polyQ neurodegenerative disorders, a group that also includes Huntington's disease [5].

The size of this expanded CAG repeat correlates well with the age of disease onset, however the CAG-repeat length is not associated with disease progression or the severity of the disease[2].

A pathological feature shared by all polyglutamine (polyQ) diseases, including SBMA, is the formation of intranuclear inclusions composed of misfolded polyglutamine-expanded proteins [6]. The accumulation of the polyglutamine-expanded AR triggers several downstream molecular events leading to dysfunction and eventual cell death [7].

In SBMA, the mutant androgen receptor (AR) protein does not only loses it function-which explains endocrine manifestations but what's more undergoes a toxic gain of androgen-dependent function.This toxic gain of function is central to disease progression as it alters the protein structure in a way that makes the receptor damaging to motor neurons and muscle tissue. This is based on the finding that other mutations that cause loss of AR function result in a different phenotype, with feminisation but not the progressive weakness and motor neuron loss of SBMA [2].

Clinical manifestations

SBMA, also known as Kennedy's disease, is a rare X-linked neuromuscular disorder that primarily affectis lower motor neuron caused by a CAG trinucleotide repeat expansion in the androgen receptor gene [6]. SBMA is characterized by a wide range of clinical manifestations [4]. The disease typically has a gradual onset, most often between the ages of 30 and 50 years [8].

As SBMA is defined by the degeneration of lower motor neurons (LMNs) in the brainstem and spinal cord [8], the principal symptom is progressive muscle weakness and atrophy. It predominantly affects proximal muscles, especially in the lower limbs, resulting in difficulties with activities such as climbing stairs or rising from a seated position [5]. This weakness can be exacerbated by cold exposure or fatigue [7]. Fasciculations, particularly in the facial muscles, tongue (a clinical hallmark), and perioral region (manifesting as a "quivering chin"), are also common [6].

Bulbar involvement is a significant clinical feature, typically presenting in the later

stages [9]. It results from degeneration of bulbar motor nerves - VII, IX, X, XI, and XII, which control muscles responsible for speech, swallowing, and facial movements. This degeneration leads to dysarthria, dysphagia, and weakness of the facial, pharyngeal, and lingual muscles [7].

Postural and kinetic tremors, predominantly of the hands, are common early central nervous system (CNS) manifestations and may precede overt muscular weakness [4]. Muscle cramps are also frequently reported early in the disease course[9]. Signs of upper motor neuron involvement, such as hyperreflexia or spasticity, are typically absent[4].

Patients may also exhibit mild to moderate sensory disturbances, mainly involving vibration sense and resulting in numbness or tingling, particularly in the distal extremities [10]. CNS involvement may extend beyond the motor system, with some patients displaying mild cognitive impairment and frontotemporal neuropsychological deficits, including impairments in verbal fluency, concept formation, and memory [4].

A hallmark non-neurological feature of SBMA is partial androgen insensitivity, attributed to loss-of-function mutations in the androgen receptor (AR) gen e[9]. These features may emerge in adolescence, often preceding motor symptoms, and include gynecomastia, testicular atrophy, infertility, and erectile dysfunction [2].

Systemic metabolic dysfunction is increasingly recognized as part of the disease phenotype. The mutant AR protein contributes to endocrine and metabolic abnormalities, including glucose intolerance, insulin resistance, hyperlipidemia, hypercholesterolemia, and abdominal obesity [5]. Some patients may develop cardiac abnormalities, including arrhythmias, hypertrophic cardiomyopathy-like changes, and Brugada-pattern electrocardiographic abnormalities [10].

Furthermore, sleep disturbances such as poor sleep quality, periodic limb movements during sleep, and obstructive sleep apnea (OSA) have also been documented [4].

The prevalence of key clinical symptoms in SBMA is summarized in Figure 1.

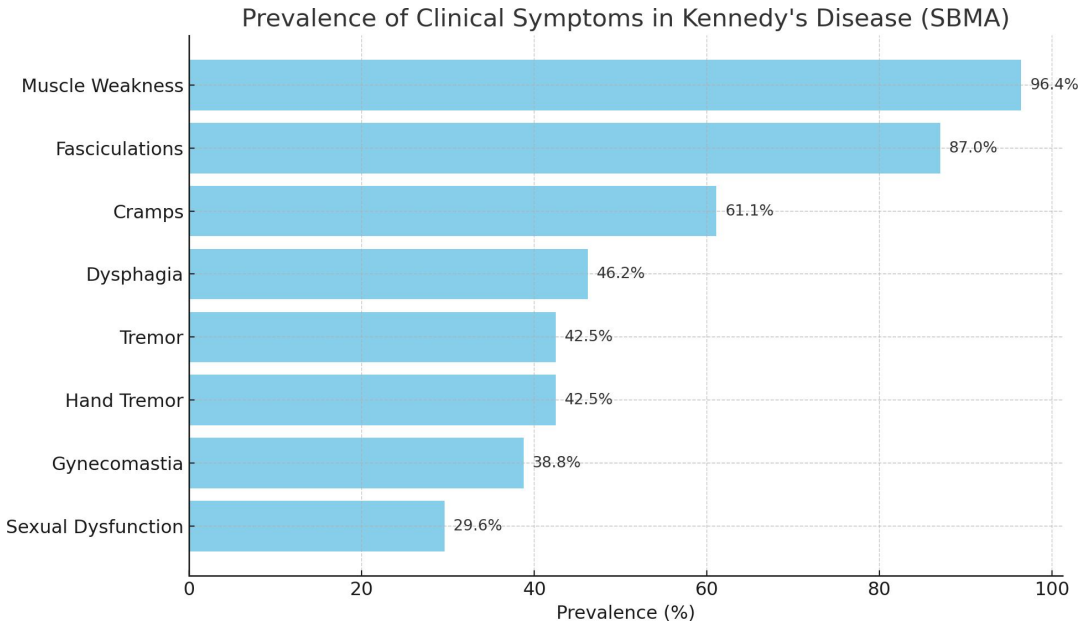

Figure 1: The prevalence of key clinical symptoms in Spinal and Bulbar Muscular Atrophy [3]

Neurological examination

Abnormal findings in neurological examination primarily indicate lower motor neuron degeneration and, less commonly, involvement of the sensory pathways and the central nervous system [4].

Progressive muscle weakness and atrophy usually affect the most proximal muscles of the limbs, especially the lower limbs [6].

Deep tendon reflexes are typically diminished or absent, and there are no pathological reflexes [4].

During cranial nerve examination, weakness and atrophy of the facial and masseter muscles, as well as tongue muscles, can be observed. Poor movement of the uvula and soft palate may also be noted [7].

A common symptom is tremor—postural or kinetic—mainly affecting the hands [5].

Sensory involvement is often manifested as a mild-to-moderate loss of sensation, especially of vibration sense, typically affecting the distal extremities [4].

Crucially, in SBMA, there is an absence of upper motor neuron involvement, which

distinguishes it from other motor neuron diseases such as ALS. Therefore, signs such as hyperreflexia, spasticity, and clonus are not typically found on neurological examination.

Additional Investigations

Laboratory investigations in SBMA may reveal elevated creatine kinase (CK) levels, indicating muscle damage [5], along with mild elevations in liver enzymes [6] and fasting glucose. A metabolic syndrome profile is frequently observed, with increased cholesterol and triglyceride levels [7]. Hormonal assessments may show low testosterone or elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, suggestive of partial androgen resistance[3].

Conventional MRI is typically unremarkable, especially in the early stages of the disease, although some patients may exhibit mild frontal lobe or brainstem atrophy . In selected cases, advanced neuroimaging techniques such as diffusion tensor imaging (DTI) can detect white matter lesions, particularly in the corticospinal tracts and limbic pathways [1].

Electromyography (EMG) commonly demonstrates evidence of chronic denervation and reinnervation in both limb and bulbar muscles, without signs of upper motor neuron involvement [4]. Nerve conduction studies may reveal mild sensory axonopathy, particularly in the distal lower extremities [11].

Polysomnography, when performed, can uncover obstructive sleep apnea (OSA), periodic limb movements, and overall poor sleep quality [13].

Diagnosis

The definitive diagnosis of SBMA is established through genetic testing [10], specifically by identifying a CAG trinucleotide repeat expansion of ≥38 repeats in the androgen receptor (AR) gene on the X chromosome[5]. This is typically conducted via PCR-based DNA analysis and can also be used to identify carrier status in female relatives[10].

Treatment

Currently, there is no cure or definitive disease-modifying treatment for SBMA. Therefore, management primarily focuses on supportive care aimed at maximizing functional capacity, minimizing complications, and improving quality of life. A multidisciplinary approach is essential.

Regular neurological evaluations are recommended once a year, to monitor motor decline and detect emerging complications. Physical and occupational therapy play a critical role in maintaining mobility, reducing fall risk, and guiding the use of assistive devices such as walkers, braces, or wheelchairs[10]. Moderate-intensity aerobic and functional exercise is generally well-tolerated and may help preserve physical function[12]; exercise regimens should be individualized and adjusted over time with input from a physiatrist[13].

Neurologopedic care, encompassing both speech and swallowing therapy, is a vital component of SBMA management. Interventions should begin with the onset of bulbar symptoms and continue as the disease progresses. Nutritional assessment is also crucial—particularly when
bulbar dysfunction or metabolic syndrome is present—to prevent both malnutrition and obesity. In cases of progressive dysphagia, gastrostomy may be considered to ensure safe and adequate nutritional intake.[5]

Pulmonary function monitoring is advised, especially in advanced stages, to assess respiratory involvement. Additionally, genetic counseling should be offered to patients and their families to support informed decision-making regarding family planning and carrier status[10].

Although no pharmacologic cure is currently available, several agents have been explored in clinical trials . Leuprorelin, an androgen-reducing agent, has shown modest benefit in delaying functional decline and improving swallowing in certain subgroups and is approved for use in Japan, though its global adoption is limited by inconsistent trial results. Dutasteride, a 5α-reductase inhibitor, did not significantly improve muscle strength but was associated with reduced fall frequency and improved quality of life in some patients. Clenbuterol, a β_2-agonist, demonstrated

improved walking capacity and pulmonary function in pilot studies, though further research is needed to confirm these findings.[2]

Conclusions

SBMA, also known as Kennedy's disease, is a rare X-linked neuromuscular disorder that primarily affects lower motor neuron caused by a CAG trinucleotide repeat expansion in the androgen receptor gene. During disease progression, a toxic gain of androgen-dependent function occurs.

Hand tremor and gynecomastia are frequently among the earliest manifestations, whereas muscle weakness and plegia usually develop later in the disease course [13]. Beyond motor symptoms, patients frequently experience sensory disturbances, mild cognitive impairment, and endocrine dysfunction linked to androgen insensitivity. Additionally, metabolic and cardiac abnormalities, along with sleep disturbances, are increasingly recognized as part of the disease spectrum.

The diagnosis involves a neurological examination alongside laboratory tests indicating muscle damage, metabolic abnormalities, and hormonal dysfunction. Definitive confirmation is achieved through genetic testing, which identifies CAG repeat expansions in the androgen receptor gene.

While a curative treatment remains elusive, the optimal management of SBMA relies on a personalized, multidisciplinary strategy including physical and occupational therapy, neurologopedic interventions, nutritional assessment, and pulmonary monitoring to optimize function and minimize complications. While no cure exists, emerging molecular and genetic therapies hold promise for future treatment advancements.

DISCLOSURE

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