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Spinal and Bulbar Muscular Atrophy – Genetic Causes, Clinical Presentation and Treatment Perspectives

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ABSTRACT

Introduction and Purpose:

Spinal bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare genetic disorder characterized by progressive muscle weakness and atrophy. The purpose of this review is to provide a comprehensive understanding of SBMA, including its pathophysiology, clinical presentation, diagnostic tools, and therapeutic approaches. By examining the latest research findings, we aim to highlight the challenges inherent in managing SBMA.

Material and method:

For this review, we performed searches across multiple databases, including PubMed, Elsevier, Medline, and Google Scholar.

Description of the State of Knowledge:

SBMA arises from mutations in the androgen receptor (AR) gene, leading to the accumulation of toxic proteins and subsequent neurodegeneration. Clinical manifestations primarily involve muscle weakness, tremors, and difficulties with speech and swallowing, with symptoms typically appearing in mid-life. While no treatment currently modifies disease progression, symptomatic management and supportive care play crucial roles in enhancing quality of life for affected individuals. Recent research has focused on understanding the underlying mechanisms of SBMA and developing targeted therapies to address them. However, challenges remain in translating these findings into effective treatments.

Conclusions:

SBMA represents a complex and challenging neurodegenerative disorder with significant implications for affected individuals and their families. While our understanding of SBMA has advanced in recent years, much remains to be elucidated regarding its pathophysiology and optimal management strategies. Continued research efforts are essential to develop novel therapeutic interventions that can effectively target the underlying mechanisms of SBMA and improve outcomes for patients.

Keywords: "Spinal and Bulbar Muscular Atrophy", "SBMA", "Kennedy's disease", "CAG repeat", "Androgen receptor gene"

INTRODUCTION

Spinal bulbar muscular atrophy (SBMA), commonly referred to as Kennedy's disease, is an X-linked recessive disorder impacting motor neurons [1]. It is characterized by the presence of more than 38 CAG repeats within the androgen receptor (AR) gene [2,3]. Due to the gene's location on the X chromosome, females who carry the gene most commonly do not develop any symptoms, but sometimes may experience distal motor deficits, cramping, and/or fasciculations, while men tend to suffer more severely from the condition [4]. The main symptoms of Kennedy's disease are associated with damage to the lower motor neuron: progressive muscle weakness and atrophy, as well as fasciculations [2,3,5]. They primarily affect the facial muscles, articulatory and swallowing muscles, larynx, and limb muscles, typically with a predominance in distal segments. The initial symptoms typically appear between the ages of 30-40 years and are nonspecific; muscle cramps and pains occur, often with positional tremors of the upper limbs. Muscle strength weakness typically appears around the fourth decade of life, is asymmetrical, and primarily involves the lower limbs [5,6]. Patients complain of difficulties in climbing stairs and rising from a seated position, as well as quick fatigue, for example, during walking. In the later course, usually after the age of 50, there is impairment of distal muscle function and weakness of the upper limb muscles. Distal symptoms worsen over time, leading to swallowing disorders and even periodic apneas due to laryngeal muscle cramps (laryngospasm) [7]. Clinical signs of upper motor neuron involvement are not observed. Nearly 60% of patients experience paresthesias, and sensory disturbances in vibration sensation in the lower limbs are common. Additionally, many patients present with symptoms of androgen resistance syndrome, such as gynecomastia, decreased fertility, testicular atrophy, and impotence. These symptoms may precede the onset of neurological disorders by several years. The occurrence of symptoms of androgen dysfunction accompanying neurological disorders may expedite the diagnosis of the disease [8,9].

AIM

This review aims to explore Spinal bulbar muscular atrophy, encompassing its pathophysiology and the latest advancements in diagnostic and therapeutic approaches. Our objective is to spotlight the challenges inherent in this condition and the ongoing efforts to tackle them.

MATERIAL AND METHODS

For this review, we performed searches across various databases such as PubMed, Elsevier, Medline and Google Scholar to identify scientific literature with up-to-date knowledge of the pathophysiology, clinical presentation and diagnostic tools and treatment strategies available for SBMA. The keywords used included "Spinal and Bulbar Muscular Atrophy", "SBMA", "Kennedy's disease", "CAG repeat" and "Androgen receptor gene". Only articles written in English were selected. The studies were meticulously examined for their relevance to the subject of this review.

CURRENT STATE OF KNOWLEDGE

PATHOPHYSIOLOGY

Spinal bulbar muscular atrophy originates from expansions of CAG repeats within the AR gene, causing the elongation of polyglutamine (polyQ) chains in the AR protein. Healthy individuals typically have repeat lengths ranging between 11 and 36 CAGs. When the number of CAG trinucleotide repeats surpasses 38, it results in the formation of a pathological protein called polyQ-AR [3]. As a result, SBMA is classified among polyQ neurodegenerative disorders, which include Huntington's disease, dentatorubral-pallidoluysian atrophy (DRPLA), and six types of spinocerebellar ataxias [10]. Although polyQ diseases vary clinically, they share several common traits. These conditions commonly emerge in mid-life, despite the proteins associated with the diseases being expressed from early development throughout adulthood. Moreover, they are characterized by the accumulation of misfolded proteins, observed as micro-aggregates (amyloid fibrils) and inclusion bodies, which are recognized as a hallmark of neurodegeneration. Protein misfolding and aggregation are not confined to neurons but also occur in peripheral tissues like skeletal muscle. These abnormal protein formations are often considered a defining feature of SBMA and other neurodegenerative disorders [11,12]. Before pathological abnormalities appear in the spinal cord in a knock-in mouse model of SBMA, there are detectable histological and molecular signs of muscle pathology. Additionally, muscle biopsy samples from SBMA patients may display a combination of myopathic and neurogenic features [13,14]. In SBMA, similar to other polyglutamine diseases, there's an existing inverse correlation between the length of the CAG repeat and the age of onset, and a direct correlation with the severity of the disease, adjusted by the age of examination [15]. In contrast to other polyglutamine diseases where the normal function of the disease protein may be unclear, in SBMA, the disease protein has a well-defined role as a ligand-dependent transcription factor. The androgen receptor (AR) functions as a nuclear hormone receptor and remains in the cytoplasm while inactive, forming a complex with heat-shock proteins. Upon binding with its natural ligands, testosterone and its more potent derivative dihydrotestosterone, various events unfold, including post-translational modification of AR, its nuclear translocation, and DNA

binding. These alterations ultimately lead to AR-mediated activation or repression of target genes [16].

Mutations in AR can be classified into loss-of-function (LOF) and gain-of-function (GOF) categories. LOF mutations, including gene deletions and missense mutations, cause androgen insensitivity syndrome. In contrast, GOF mutations, such as gene amplifications and missense mutations, can lead to hirsutism, prostate hyperplasia, and prostate cancer through hypermorphic and neomorphic mechanisms. Neurodegeneration in SBMA is linked exclusively to CAG repeat expansions in the AR gene [3]. Patients with androgen insensitivity syndrome do not experience motor neuron degeneration or muscle atrophy, whereas those with SBMA show mild androgen insensitivity. This suggests that CAG expansions in AR contribute to neurodegeneration through a combination of toxic GOF and partial LOF mechanisms [17]. Mouse models with expanded polyglutamine AR protein closely replicate the human disease, exhibiting lower motor neuron specificity and gender specificity. However, a partial loss of normal AR function may also contribute to the disease, as SBMA patients often display mild signs of androgen insensitivity, such as gynecomastia and decreased fertility [14, 18].

A key feature of polyglutamine diseases is the presence of protein inclusions in the nucleus and cytoplasm. These inclusions are made up of disease proteins that are tagged with ubiquitin and associated with various transcription factors, chaperones, and components of the proteasome [19]. In SBMA muscle, there is an unexpected reduction in the expression of genes encoding about 30% of the constitutive proteasome subunits and 20% of E2 ubiquitin-conjugating enzymes [20]. This extensive downregulation is associated with decreased levels of the proteasome transcription factor NRF1/NFE2L1. Both active NRF1 and the aspartyl protease DDI2, which is essential for NRF1 cleavage and nuclear translocation for gene regulation, are significantly reduced in SBMA muscle [21]. The degradation of polyQ AR primarily occurs through the ubiquitin-proteasome pathway and that reduced proteasome function in SBMA muscle leads to the accumulation of toxic polyQ AR species [22, 23].

Mitochondrial impairment and oxidative stress are proposed as causative factors in polyglutamine diseases. Depolarization of the mitochondrial membrane and elevated reactive oxygen species levels have been observed in SBMA models. Changes in muscle function have been observed, impacting the ability of muscles to contract efficiently. It is caused by the pathogenic AR protein that suppresses the transcription of PGC-1 subunits, co-activators regulating nuclear-encoded mitochondrial proteins, contributing to mitochondrial dysfunction and oxidative stress [24, 25].

The pathogenic AR protein inhibits the transcription of subunits of peroxisome proliferator-activated receptor gamma co-activator (PGC-1), a transcriptional co-activator that regulates the expression of mitochondrial proteins encoded by nuclear genes [25]. This suppression leads to mitochondrial dysfunction and oxidative stress.

Axonal transport obstruction is another factor in SBMA neuronal dysfunction. In SBMA model mice and patients, neurofilaments and synaptophysin accumulate at the distal ends of motor axons, indicating problems with retrograde axonal transport. The pathogenic AR protein disrupts axonal transport by activating cJun N-terminal kinase (JNK) activity and dysregulating the transcription of dynactin 1, an axonal motor protein. Disruption of retrograde axonal transport has been observed in SBMA mouse models, although this finding is not consistent across all models [26, 27, 28].

CLINICAL PRESENTATION

SBMA primarily affects men. The first symptoms typically manifest between the ages of 35 and 50 years, rarely appearing in childhood or adolescence [29]. Women are usually asymptomatic carriers of SBMA. They typically transmit the disease without showing symptoms. Only a minority of female carriers, particularly those with 38 or more CAG repeats, may experience mild symptoms such as cramping or tremors. These women generally do not exhibit significant motor neuron disease [30,31]. The earliest symptom typically experienced is a mild postural hand tremor, difficulty walking and a tendency to fall [8]. Head, voice, and lower limb tremors may also occur. These tremors are often responsive to alcohol and can be influenced by load bearing and posture. Muscle weakness is a key clinical characteristic of SBMA, appearing in 97% of cases. Lower limb debility is the most common symptom prompting patients to seek hospital treatment [12, 32]. It should be noted that in the early stages of the disease, muscle weakness in the lower limbs is typically more proximal than distal. This distinction can serve as a clinical clue in the differential diagnosis from distal hereditary motor neuropathies (dHMN) [33]. Higher CAG repeat numbers are linked to an earlier onset but not to the rate of progression. Over time, muscle atrophy becomes evident in both proximal and distal muscles, with about one-third of affected individuals requiring a wheelchair approximately 20 years after the onset of symptoms. Some patients may also experience degeneration of the dorsal root ganglia, leading to mild-to-moderate sensory abnormalities [8, 34]. Sensory symptoms, such as numbness and tingling, are also reported primarily in the distal limbs in more than half of SBMA patients, though these symptoms typically appear later in the disease course [34]. Although the autonomic nervous system is not typically considered part of Kennedy's disease, there is evidence suggesting that it may be subclinically involved [35].

As the disease progresses, involvement of the bulbar muscles leads to difficulties with speech and swallowing. It manifests as fasciculations of the tongue with midline furrowing due to glossal muscle wasting, fasciculations and myokymia of the perioral region, dysarthria, and dysphagia [36,37]. Dysphagia is present in almost 80% of SBMA patients, particularly in the later stages of the disease [37]. Some patients also experience laryngospasms [38]. Twitching movements of the chin (perioral fasciculations-myokymia), known as a "quivering chin," may occur due to spontaneous motor unit discharges or voluntary contractions of the perioral muscles [39]. Perioral fasciculations are also a significant clinical clue to the diagnosis of Kennedy's disease, especially when associated with other characteristics of the condition, such as proximal muscle atrophy and gynecomastia [40]. Severely affected individuals, who are often non-ambulatory, are at risk for aspiration pneumonia and respiratory failure due to weakened bulbar and respiratory muscles [41]. However, most individuals with SBMA have a normal life expectancy and do not die from direct complications of motor neuron disease [42].

Symptoms of androgen insensitivity typically begin in adolescence with gynecomastia, which is frequently observed in affected males [43]. There is variability in disease severity and progression both within and between families [44,45]. This variability is particularly evident in androgen insensitivity signs such as testicular atrophy and oligospermia/azoospermia, which lead to reduced fertility. Males with SBMA may struggle to grow a thick beard and may have difficulty conceiving. The concern over androgen insensitivity can be greater for affected individuals than motor neuron disease, especially in the early stages of the disorder [45].

Cardiological investigations reveal that some individuals with SBMA develop abnormal cardiac rhythms and may occasionally show changes similar to hypertrophic cardiomyopathy [46,47]. While the pathological significance of these findings is unclear, there is a growing

recognition that most individuals with SBMA exhibit metabolic dysregulation [48]. Total cholesterol, LDL, and triglycerides are typically elevated, and diabetes frequently coexists in SBMA patients across multiple studies, suggesting the presence of a partial metabolic syndrome in these individuals. These findings often qualify such individuals for a diagnosis of non-alcoholic fatty liver disease [49,50].

In a recent study, it was found that SBMA patients were more prone to experiencing moderate to severe lower urinary tract symptoms (LUTS) in the absence of benign prostatic hyperplasia [51]. Reduced levels of androgens have been associated with a higher likelihood of bladder outlet obstruction, and hypogonadism is a notable factor connecting metabolic syndrome with urinary symptoms although the precise mechanism of these remains uncertain [51].

MANAGEMENT

Currently, there is no available treatment to modify the progression of the disease. Management of SBMA should prioritize enhancing mobility and function while preventing complications of the disease. The primary approach to treatment is providing symptomatic support, which includes pain management, physiotherapy, speech therapy, and, in some cases, gastrostomy [4]. Although the benefits of multidisciplinary management have not been systematically assessed in clinical trials, empirical evidence suggests significant advantages. There are currently no established best practice recommendations for KD at the national, European, or international levels [4, 52].

Kennedy's disease patients typically experience a slow progression of the condition, with mobility preserved until the advanced stages of the disease [8]. The use of a wheelchair typically begins around the age of 60 years [32]. Tailored exercises adapted to each patient's functional level and preventive measures are recommended to reduce the risk of aspiration and improve mobility in SBMA patients. However, the precise role of exercise remains unclear, and various studies have not shown significant effects [53,54]. Further research is required to assess the potential benefits of functional exercise.

Androgen reduction therapy has been effective in animal models that replicate the disease phenotype [55]. However, clinical trials testing androgen-reducing agents such as leuporelin and dutasteride in randomized, placebo-controlled settings have not shown significant effects on the primary outcome measures of swallow function and muscle strength [55,56,57,58].

Additional treatment strategies aimed at directly enhancing muscle function, either through exercise or through the use of anabolic drugs like clenbuterol [59,60], have yielded disappointing results. A recent study evaluated the safety, tolerability, and preliminary efficacy of an IGF-1 mimetic, but treatment was associated with a high incidence of immunogenicity and showed no clear improvement in muscle function [61].

For gynecomastia, treatment options include breast reduction surgery as necessary. Regarding cardiac and other manifestations, standard treatment protocols are typically followed under the guidance of a cardiologist and/or endocrinologist. Additionally, monitoring blood sugar, lipids, and cholesterol levels is recommended to assess for insulin resistance and non-alcoholic fatty liver disease [3].

It is advisable to determine genetic risk and discuss the availability of prenatal or preimplantation genetic testing before pregnancy. Offering genetic counselling, including conversations about potential risks to offspring and reproductive options, to young adults who are affected, carriers, or at risk of being carriers is appropriate. In families with an identified AR CAG trinucleotide repeat expansion in an affected member, prenatal testing and preimplantation genetic testing for SBMA become feasible options [3].

CONCLUSIONS

Spinal and Bulbar Muscular Atrophy is a multifaceted and demanding neurodegenerative condition. The implications of SBMA are profound, affecting various aspects of life and requiring comprehensive care and support. Over recent years, scientific research has made strides in enhancing our comprehension of SBMA. However, a considerable amount of knowledge still needs to be uncovered, particularly concerning the intricate mechanisms driving its pathophysiology and the best strategies for managing the disease.

Through dedicated and ongoing research efforts, there is hope that new therapeutic interventions can be developed. These interventions would ideally target the root mechanisms of SBMA, offering more than just symptomatic relief but potentially altering the disease course and improving long-term outcomes for patients. Continued investment in research is crucial to achieve these advances and make a meaningful difference in the treatment of SBMA.

DISCLOSURES

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