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Spinal and Bulbar Muscular Atrophy

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Synopsis

Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a slowly progressive X-linked neuromuscular disease caused by a trinucleotide (CAG) repeat expansion in the androgen receptor (AR) gene. Affected males typically develop weakness in their mid-forties, as well as evidence of androgen insensitivity with reduced fertility and gynecomastia. Diagnosis is often delayed because of decreased awareness of the disease, although genetic testing allows direct diagnosis of the disease. Therapeutic strategies to block the function of the mutant androgen receptor have been unsuccessful thus far, and evaluation of additional candidate therapies is underway.

Key Terms

Spinal and bulbar muscular atrophy; Kennedy's disease; motor neuron disease; androgen receptor

Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease,[1] is caused by progressive degeneration of the lower motor neurons and muscle. A trinucleotide (CAG) repeat expansion in the androgen receptor (AR) gene on the X chromosome is the cause.[2] Repeat lengths of 38–68 CAGs have been reported in patients, with 11–32 CAGs in normal individuals.[3–5] Affected males typically develop symptoms and findings in the limb and bulbar muscles with weakness, atrophy, and fasciculations. Bulbar weakness indicates NP8/MP7 overlap ("Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS" in this issue). The age of onset correlates inversely with the length of the CAG repeat,[6] with earlier age of onset in those with longer repeats. The disease has been widely reported in European, Asian, and American populations.

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Mechanism

The CAG repeat is expressed as an expanded polyglutamine tract in the AR, and studies in animal models and patients indicate that androgen dependent gain of function by the receptor results in toxicity of the mutant protein.[7,8] Unlike other polyglutamine diseases in which the native function of the disease protein in unclear, the function of the AR has been well characterized. In the absence of androgen, the receptor is localized in the cytoplasm and bound to heat shock proteins. Testosterone or dihydrotestosterone binding by the receptor results in nuclear translocation and binding to androgen responsive elements throughout the genome.[9] Translocation of the mutant AR into the nucleus also appears to be necessary for toxicity, as deletion of the nuclear localization signal prevents toxicity in a mouse model.[10] The features of disease result from a loss as well as gain in function of the receptor since patients often have gynecomastia and reduced fertility in addition to weakness and muscle atrophy. The mutated receptor has a propensity to aggregate and form inclusions in tissues where it is expressed.[11] Toxicity of the mutant AR is likely mediated through transcriptional dysregulation,[12] with disruption of mitochondrial function,[13] protein homeostasis,[14] and cellular signaling.[15] The transcriptional co-activator CBP is sequestered and depleted in SBMA and other polyglutamine diseases.[16] Defects in autophagy, the cellular process responsible for degrading and recycling cellular constituents, has been implicated in SBMA pathology.[17] Alteration of autophagy through genetic and pharmacological mechanisms has been shown to be protective in several models of the disease.[18]

Although the AR is expressed in various tissues throughout the body, the predominant site of toxicity is in the spinal cord and muscle. Brainstem motor nuclei are also susceptible, except for the third, fourth, and sixth cranial nerves. Loss of anterior horn cells in the spinal cord has been described,[19] and a direct role of the mutant AR in muscle degeneration has been demonstrated in animal models of the disease.[20] Several studies have reported that selective expression or correction of the mutant AR in mouse muscle can reproduce or ameliorate the disease manifestations, respectively.[21,22] The relative contributions of the motor neuron and muscle towards the pathogenesis in patients remains to be defined. Affected males can also experience mild sensory loss in the distal extremities from degeneration of dorsal root ganglion cells.

Disease Course

The average age of onset is usually in the mid 40s, with a range of 18 to 64.[4] Clinical features of the disease can vary among affected individuals in the same family. Weakness affects the upper and lower extremities, following NP7 with both proximal and distal muscles (see in this issue (“Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS”). Features of androgen insensitivity such as sexual dysfunction, gynecomastia, and testicular atrophy may be apparent before motor involvement. Overall, the most common presenting features are weakness, tremor, and cramping.[3,4] The progression of weakness in the disease is slow, with an approximately 2% decrease in muscle strength by quantitative muscle testing (QMT) per year.[23] Patients may experience a stepwise drop in performance as critical thresholds needed for function tend to be more readily perceived as function is lost. SBMA patients generally have good

preservation of mobility until late in the disease, requiring a cane or other assistive device at a median age of 60. Those with progressive loss of gait and balance function may eventually require a wheelchair. Bulbar manifestations, including dysarthria and nasal speech, can present early in the disease course and may progress to dysphagia. There are subtle to prominent tongue and facial muscle fasciculations whereas limb fasciculations are not prominent. Patients with advanced disease may develop difficulty managing secretions with the risk of aspiration pneumonia.[3] The average life expectancy is reduced as a result of bulbar and respiratory muscle weakness, although many subjects have a normal life span. Muscle stretch reflexes are absent or reduced. There are often subclinical vibratory changes in the legs more than the arms coupled with reduction of sensory nerve action potential (SNAP) amplitude on nerve conduction studies.

The CAG repeat size has been found to correlate with clinical features of the disease.[3,4,24] A larger CAG repeat is associated with earlier disease onset and earlier age for requiring the use of a handrail, cane, or wheelchair. The rate of progression of the disease was not significantly influenced by CAG repeat length in a natural history study of 223 subjects.[3] Although patients with larger CAG repeat lengths reach loss of function milestones faster, the rate of decline between milestones does not appear to be affected by the CAG repeat size alone.

Diagnosis

Genetic testing is the preferred method for making a diagnosis, with all SBMA patients having a CAG repeat expansion of at least 38 CAGs. Variation in the CAG repeat length can be seen among affected members of the same family.[6,25] The serum creatine kinase (CK) level in most patients is usually elevated to 2–4 times the upper limit of normal, up to 900–1400 U/L.[3,4] Liver enzymes are also often found to be abnormal, with mild elevation in aspartate and alanine aminotransferase levels. Additional investigations are currently ongoing to evaluate liver dysfunction in the disease. In a study of 144 Japanese subjects with SBMA, 12% were found to have a Brugada-type electrocardiogram with a coved or saddle-back-type ST-segment elevation in more than one right precordial lead.[26] Additional studies are needed to determine whether this finding is present in other patient populations.

A family history helps in making the diagnosis, as a majority of subjects have other affected relatives. As an X-linked disease, SBMA generally affects men, and may be transmitted through asymptomatic females. Cramping and other symptoms have been reported in a minority of female carriers.[27] A genetic diagnosis should ideally be established in an affected family member before testing unaffected family members.

On examination, lower motor neuron signs are typically found, including muscle atrophy, fasciculations, and decreased or absent deep tendon reflexes. The weakness often initially occurs in the lower extremities.[4,24] Distal loss of sensation for various modalities may be noted on examination. Over 90% of SBMA patients have low SNAP amplitudes on nerve conduction study.[4] The motor unit nerve estimation (MUNE) is reduced to about 50% of healthy control values in the abductor pollicis brevis muscle.[28] Muscle biopsy may show

evidence of both myopathic (central nuclei, myofibrillar disorganization) and neurogenic (fiber type grouping, angulated fibers) changes.[29]

The availability of genetic testing has helped to standardize the diagnosis of SBMA. Many patients are misdiagnosed with amyotrophic lateral sclerosis (ALS) before receiving the correct diagnosis.[4] Unlike SBMA, individuals with ALS have upper motor neuron signs such as hyperreflexia and spasticity. The disease course in ALS is also more rapidly progressive with greater asymmetry. SNAP amplitudes are lower in SBMA compared to ALS,[30] providing another useful tool in the differential diagnosis of these two diseases. SBMA may also be mistaken for other neuromuscular disorders such as myasthenia gravis, chronic inflammatory polyneuropathy, polymyositis, and metabolic myopathy. SBMA should be considered in patients thought to have myasthenia who are antibody negative and do not improve on therapy.

Clinical Case

A 45 year old male presented with a 9-month history of progressive leg weakness. The weakness is symmetrical and has led to impairment of walking and difficulty with balance on uneven surfaces. He has also had recent choking spells and mild paresthesias in the distal lower extremities.

Examination is remarkable for gynecomastia. He has a nasal, airy voice with fibrillations in the tongue, decreased movement of the palate and reduced posterior pharyngeal wall contraction. Fasciculations are seen in the chin. Mild atrophy in the first dorsal interosseous is appreciated in both hands, with mild weakness in these muscles. Light touch and vibratory sensation are reduced in both lower extremities in a gradient distribution and reflexes are diminished throughout. No upper motor neuron signs are present. On gait testing he has mild difficulty squatting and with tandem gait.

On laboratory testing he has elevation of CK to 950 U/L. Electrophysiology studies show decreased motor unit number estimation, positive sharp waves, and reduced sural sensory nerve amplitudes. Genetic testing for the CAG repeat expansion in the AR gene shows a repeat size of 45 CAG, and further discussion of the family history identifies a male maternal cousin with a similar history.

Management

Management of SBMA is focused on preventing complications of the disease such as falls, fractures, aspiration, and reduced mobility. There is currently no effective treatment to prevent progression of the disease. Those at risk for dysphagia should undergo a swallow study to identify risks of aspiration. Deficits in swallow function can be seen as abnormal pharyngeal retention of barium during videofluorography.[31] Exercises and precautionary measures can be recommended to reduce the risk of aspiration. A physical therapy assessment can be helpful in enhancing the mobility of patients by providing assistive devices and recommending targeted exercises for the preservation of gait and mobility.

Exercise has been demonstrated to be beneficial for many forms of neuromuscular disease.[32] The effect of 12 weeks of moderate intensity aerobic exercise was investigated in a group of eight SBMA subjects.[33] Although there was no change in maximal oxygen uptake, an increase in maximum work capacity was detected. In a separate 12 week study of 50 SBMA subjects, functional exercise was compared to stretching exercise.[34] There was no improvement in the primary outcome measure, the total adult myopathy assessment tool (AMAT) score, although post-hoc analysis showed that low functioning individuals had relative improvement in functional AMAT score. Although it is unclear what the long term effect of exercise may be on the disease progression, short term periods of exercise appear to be well tolerated. Exercise should be adjusted to the patient's level of function and titrated with input from a physiatrist.

Clinical trials in the disease have focused on reducing AR ligand. Androgen reduction with leuprorelin and castration has been shown to mitigate disease manifestations in transgenic animal models of SBMA.[35,36] Leuprorelin is a luteinizing hormone-releasing hormone analog that reduces the production of testosterone and its derivative, dihydrotestosterone. In a 48 week phase 2 study, SBMA patients on leuprorelin did not have significant improvement compared to placebo in the primary outcome measure (the ALS Functional Rating Scale), although there was evidence of increased duration of cricopharyngeal opening on videofluorography.[37] A subsequent phase 3 placebo-controlled study did not show a significant effect on swallow function, although a post-hoc subgroup analysis showed benefit in subjects with less than 10 years disease duration.[38] Another agent, the 5α-reductase inhibitor dutasteride, was evaluated in a 2 year randomized, double-blind, placebo-controlled study of 50 subjects, and it did not show an effect on the primary measure of muscle strength (Quantitative Muscle Assessment).[23]

Activation of pathways that mitigate AR toxicity has also been pursued as a therapeutic strategy. Insulin-like growth factor 1 (IGF-1) has direct anabolic effects on muscle and also increases mutant AR clearance through the ubiquitin-proteasome system.[39] Phosphorylation of the AR by Akt enhances this clearance, and activated phospho-Akt can be measured as a biomarker for agents targeting this pathway. In SBMA mice, overexpression and exogenous delivery of IGF-1 rescue behavioral and histopathological changes in the transgenic mice overexpressing mutant AR. In a recent open-label trial of the β2-agonist clenbuterol in sixteen subjects with SBMA, an increase in the 6-minute walk test and forced vital capacity was seen after 12 months of intervention.[40] Future randomized, placebo controlled studies of drugs in this class will be needed to confirm their functional efficacy.

A disease of nerve or muscle?

SBMA is considered primarily a disease of the motor neuron. Degeneration of motor neurons is seen in the anterior horn of the spinal cord from patients, and evidence of motor neuron dysfunction is seen in electrophysiology studies, with a reduction in motor unit number estimation (MUNE).[4] Abnormalities in motor neuron cell models of the disease have also been reported.[41,42] Recently, there has been increasing evidence that muscle also plays a role in the disease process. A knock-in mouse model of SBMA has histological and molecular signs of muscle pathology before the appearance of pathological changes in the

spinal cord.[20] Transgenic mice that selectively overexpress the normal AR in muscle have also been found to have pathological findings similar to transgenic mice with overexpression of the mutant AR.[43]

A conditional mouse model of the disease has been helpful in identifying tissue specific contributions to the disease.[21] In this model, a full-length human AR transgene with 121 CAG repeats was expressed under the control of the endogenous AR promoter. The transcriptional start site of the promoter was flanked by loxP sites, allowing its removal with Cre recombinase, thus effectively knocking out expression of the mutant gene in specific tissues. With this model, muscle specific knockout of the mutant androgen receptor significantly ameliorated the disease phenotype despite continued expression of the mutant AR in the spinal cord. Antisense oligonucleotides (ASOs) have been investigated as potential therapeutic agents to knock down expression of the mutant AR in mice. Disease manifestations in knock-in mice were rescued with subcutaneous delivery of the ASO to decrease expression in the muscle. Intraventricular delivery of the ASO to reduce AR expression in the spinal cord did not affect the disease manifestations in these mice.[22]

In clinical trials, the site of the disease pathogenesis is an important factor in choosing the optimum route of delivery for the intervention being tested. Animal studies indicate that the muscle may be playing an important role in the disease mechanism. Future studies are needed to define how the muscle deterioration is affecting the disease process in patients and to understand the interaction between motor neuron and muscle in SBMA.

Conclusions

SBMA is caused by a polyglutamine repeat expansion in the AR, and it is inherited in an X-linked pattern. Neurological symptoms usually begin in the early to mid 40s, with weakness as a predominant feature of the disease. Manifestations of the disease likely result from both gain and loss of function of the androgen receptor. Although no therapy currently exists to prevent progression of the disease, supportive intervention may improve mobility and prevent complications. Mild to moderate exercise is safe, however subjects who exercise have not been found to significantly improve muscle strength or function. Randomized, placebo-controlled clinical trials of androgen reduction therapy have not shown significant effects on primary outcome measures. Expressing the mutant AR in a restricted tissue specific manner in mice has helped to establish the muscle as a primary site for the disease. Studies are ongoing to identify and evaluate new therapeutic strategies in disease models and patients.

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Key points

Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disorder with degeneration of lower motor neurons and muscle resulting in slowly progressive weakness, atrophy, and fasciculations.

Genetic testing of a CAG trinucleotide repeat in the androgen receptor gene confirms the diagnosis. Laboratory testing of serum creatine kinase (CK) and electrophysiology studies are frequently abnormal, and testing of swallow function may help in identifying those at risk of developing aspiration.

There is currently no effective therapy to prevent progression of the disease, and management is focused on preventing complications and improving mobility and function.