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Progressive Proximal Spinal And Bulbar Musclar Atrophy Of Late Onset

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Keywords:- CAG = is the codon that codes for the Lipid acid, ADL = activities of daily living; CI = confidence interval; CMAP = compound motor action potential; IIEF = International Index of Erectile Function questionnaire; MCS = mental component summary of the SF-36v2; MUNE = motor
unit nerve estimation; NIH = the National Institutes of Health; PCS = physical component summary of the SF-36v2;QMA = quantitative muscle assessment; SBMA = spinal and bulbar muscular atrophy; SD = standard deviation; SE = standard error;SF-36v2 = Medical Outcomes Study 36-item Short Form Version 2 questionnaire; SNAP = sensory nerve action potential.

Abstract:-

Progressive spinal muscular atrophy, juvenile proximal spinal muscular atrophy "Kugelberg-Welander", and infantile muscular atrophy "Werdnig-Hoffman" comprise a group of diseases by virtue of their pathological similarity. Chronic degeneration of the lower motor neurons and neurogenic atrophy of the skeletal muscle are common to all. The diseases differ in mode of inheritance, age of onset, distribution of muscular atrophy, and prognosis. Some investigators have considered them as a continuum of the same disease, underscoring the pathological similarity, while others have emphasized the clinical differences and prefer to regard them as distinct entities. In describes 2 families in which 11 members, all male, were affected by an unusual, slowly progressive spinal and bulbar muscular atrophy. This disease, apparently inherited as a sex-linked recessive trait, becomes manifest clinically in the fourth and fifth decades and initially involves proximal muscles.The proximal weakness gave a clinical picture similar to muscular dystrophy in some patients. A full description is made of the prepositus of each family, but only the more striking features or unusual aspects in other cases.(1)

Motor neuron diseases are progressive neurologic illnesses that selectively affect the anterior horn cells in the spinal cord and cranial nerve motor neurons, resulting in their loss. Spinal muscular atrophy (SMA) is a distinctive group of autosomal-recessive motor neuron diseases that begin in childhood or adolescence. SMA is discussed here because the disease is commonly considered with the childhood myopathies and because the pathologic findings in skeletal muscle are characteristic.(2)

Introduction:-

Spinal and bulbar muscular atrophy is an X-linked motor neuron disease caused by a CAG repeat expansion in the androgen receptor gene. To characterize the natural history and define outcome measures for clinical trials.In USA 2009 they assessed the clinical history, laboratory findings and muscle strength and function in 57 patients with genetically confirmed disease. they also administered self-assessment questionnaires for activities of daily living, quality of life and erectile function. And they found an average delay of over 5 years from onset of weakness to diagnosis. Muscle strength and function correlated directly with serum testosterone levels and inversely with CAG repeat length, age and duration of weakness. Motor unit number estimation was
decreased by about half compared to healthy controls. Sensory nerve action potentials were reduced in nearly all subjects. Quantitative muscle assessment and timed 2 min walk may be useful as meaningful indicators of disease status. The direct correlation of testosterone levels with muscle strength indicates that androgens may have a positive effect on muscle function in spinal and bulbar muscular atrophy patients, in addition to the toxic effects described in animal models.(3)

In the development of a treatment for SBMA, early intervention may also be important to affect disease progression. The subjects in study did not seek medical attention until an average of 2 years after symptom onset, and there was an additional 3 years from first medical evaluation until a clinical diagnosis of SBMA was made. Increased knowledge about SBMA and its clinical manifestations, together with increased availability of confirmatory genetic testing, should speed the diagnosis of SBMA.The principal clinical features of SBMA in study confirm the findings of other retrospective analyses. Muscle cramps were often reported as a first symptom, but leg weakness, tremor and bulbar involvement were also common. Sixteen of 50 subjects had no known family history, which is likely to be due to inheritance through non-manifesting female carriers.The weakness affected upper and lower extremities and proximal and distal muscles similarly. A majority of the patients had some asymmetry in muscle strength,and interestingly 69% of these had greater weakness on the dominant side.

Such dominant-side predominant weakness has been described in other neuromuscular disorders, particularly facioscapulohumeral dystrophy, and it may reflect asymmetric muscle use. We found an inverse association between CAG repeat length and age at evaluation as reported previously.

Androgen levels and strength both correlated inversely with the age of the subjects in study. However, after adjusting for age or disease duration and repeat length, serum testosterone still correlated positively with muscle strength, as indicated by QMA and timed 2 min walk.In contrast to previous reports,The SBMA subjects had mean cholesterol and glucose levels similar to a national sample of men in the same age range, although 53% had elevated cholesterol and 12% increased fasting glucose levels relative to the laboratory reference standards.

Discussion:-

The SBMA population scored consistently lower in functional, physiological, and self-reported quality of life measures than age-matched healthy controls. SBMA scores resembled those reported in other impaired populations, e.g. the timed 2 min walk in 12 subjects (7 men and 5 women) with Parkinson's disease , and the IIEF scores in patients with symptomatic erectile dysfuction.

The decrease in physical function in SBMA is associated with lower scores in ADL and quality of life. The activity scores in the ADL questionnaire were decreased 5%-47% from maximal (normal).The mean ambulation velocities, both with and without gait aids, were less than what is normally required to cross a street in a pedestrian crosswalk 1.2m/s The divergence of the PCS and MCS scores points to the physical burden of SBMA and indicates the patients' relatively normal psychological wellbeing.

Reliable outcome measures will be needed to assess therapeutic efficacy in future clinical trials of SBMA. In this analysis, we examined several different measures used to quantify disease related deficits. Our cross-sectional analysis indicates that the QMA and timed 2 min walk appear promising as feasible, quantitative, and potentially meaningful measures of clinical status in SBMA. Each correlated with self-assessed quality of life as indicated by ADL,SF-36v2 and IIEF scores. The statistical MUNE may also be useful as a relatively objective, easily blinded physiological biomarker of motor neuron degeneration. Additional research will be necessary to establish the reliability and sensitivity of these measures in SBMA, and to define the clinical course of the disease prospectively.Trials of anti-androgen treatment in SBMA have been based on evidence of efficacy from animal models.

The animal studies indicate that the toxicity of the mutant androgen receptor protein in SBMA is ligand-dependent, and that reducing testosterone levels may be beneficial. However, our finding that higher, not lower, testosterone levels are associated with better muscle strength and function indicates that it may be necessary to balance the anabolic strengthening effects of androgens against any potentially deleterious effects of androgen-activated mutant androgen receptor toxicity, such as can be inferred from the animal studies. A limitation of this interpretation is that it is based on a cross-sectional analysis. The therapeutic implications are best addressed in prospective, randomized clinical trials.[(2)] Aslo from genetic way All forms of SMA are associated with a locus on chromosome 5 that harbors the survival motor neuron gene (SMN1). Homozygous deletions of SMN1 (or less commonly, intragenic mutations) occur in over 90% of patients with SMA, and contiguous deletion of the nearby neuronal apoptosis inhibitory protein gene (NAIP) may be associated with a severe clinical phenotype.The SMN gene product contains a Tudor homology region (a highly conserved motif involved in RNA processing), which is thought to be involved in spliceosome function, including removal of introns from pre-mRNA.
SBMA patients may become wheelchair dependent 20–30 years after onset. Involvement of bulbar muscles may lead to dysarthria and dysphagia. Fasciculations often occur, particularly around the mouth and in the tongue. Affected individuals frequently have muscle cramps and tremor. Other common neurological features include decreased or absent deep tendon reflexes and sensory loss. SBMA patients also often have signs of androgen insensitivity, such as gynecomastia and reduced fertility .
SBMA is a member of the family of CAG-polyglutamine expansion diseases that includes Huntington's disease and seven spinocerebellar ataxias (Lieberman et al., f 2000). Previous studies of SBMA and the other polyglutamine diseases have shown that the length of the CAG expansion correlates inversely with age of disease onset, i.e. the longer the expansion the earlier the onset. In SBMA, CAG repeat length has also been reported to correlate with motor and sensory nerve conduction abnormalities (Suzuki et al., 2008).
The SBMA repeat expansion is in the first exon of the androgen receptor gene. The androgen receptor is a nuclear receptor that normally regulates gene expression after ligand binding. The primary androgen receptor ligands are testosterone and dihydrotestosterone. Studies in animal models and patients indicate that these ligands are important for the development of the disease. This evidence includes the following observations: (i) male transgenic mice expressing the mutant androgen receptor have a neuromuscular deficit resembling SBMA and females are much less affected; (ii) when the male mice are castrated or treated with the anti-androgen leuprorelin , the phenotype is improved, and when female transgenic mice are given testosterone, the SBMA phenotype becomes fully manifested; (iii) in humans, heterozygous female carriers of the disease gene are generally asymptomatic, and even homozygous females in one reported family had only mild symptoms. Together, this evidence supports the hypothesis that SBMA disease manifestations are primarily due to a ligand-dependent toxic gain of function in the mutant[(4)].

References:-

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