WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 7, 1489-1498. Review Article ISSN 2277– 7105

SPINAL MUSCULAR ATROPHY (SMA): EXPEDITIOUS REVIEW ON THERAPEUTIC MANAGEMENT OF SMA

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Article Received on
30 April 2015,

Revised on 25 May 2015,
Accepted on 14 June 2015

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ABSTRACT

Spinal muscular atrophy (SMA) is a autosomal recessive genetic neuromuscular disorder that affects the parts of nervous system in spinal cord which control the voluntary muscles movements. As it is rare neuromuscular disorders that affect as many as 1 person in 10 in the general population. This disease caused by a genetic defect in SMN1 gene which encodes SMN (Spinal muscular neuron) which is necessary for motor neurones survival. Spinal muscular atrophy is known to be most common genetic cause of infant deaths. Common symptoms are progressive deteriorating voluntary muscles activities starts form shoulders, hips, thigh and upper back and with the time, activity of muscles of lungs and oesophagus is vanished but not manifested with less recognized any kind of cognitive impairment. Even, Canada till now does not have any promising drug therapy to treat this rare debilitating disorder without any effective clinical policies. In most western countries, only palliative therapy and genetic counselling is recommended for the patients or peoples who have family history of Spinal muscular atrophy keeping its fragile X syndrome whether they can have children or must not have. Hence, governments of all countries must have all levels for effective clinical and social policies modulation to ensure that patients as well as families affected by Spinal Muscular atrophy will have access to cost effective life-saving treatments and ethical endurance program to get their maximum benefits to improve various advanced prognostic and diagnostic techniques e.g. biochemical testing; SMA gene linkage analysis; genetic counselling; PCR-RFLP; quantitative SMN gene dose analysis; monosomal analysis used for the medical management of this disease. Hence, this smart study might be helpful to introduce the clinical

management, effective treatments, innovative approach and ethical quandary of Spinal muscular atrophy in brief.

KEYWORDS: Spinal muscular atrophy; SMA; SMN1; SMN2; motorneurons; neuromuscular disorder; spinal muscular neurons.

INTRODUCTION

Spinal muscular atrophy (SMA) is a fragile X syndrome and known as inherited neuromuscular disorder not having significant cognitive disability. It affects the normal voluntary muscles movements due to genetic impairment of SMA1 in spinal cord which is the only one director of generating nerve signals for voluntary act of muscles. It was also counted earlier the main cause of infant deaths that becomes worse with the time starts from muscle impairment of shoulder, hips, thigh, abdomen, upper back then followed by respiratory and oesphageal muscle impairment and lead to death.[1-3] Its genetic basis was first reported in 1996 to find out the potential clinical management and social ethical plight of this non-curable disease.[4-8] Various new socio-economic and research driven clinical therapeutic tools were found to be to encourage palliative and drug therapies based analogous activity for the medical management of SMA,[3, 9, 10] The spinal cord contains white matter (mostly myelinated axons) and gray matter (which contains cell bodies and unmyelinated axons). The gray matter is divided into regions called dorsal and ventral horns. Basically, motor neurons located in ventral horns are affected in SMA and responding weak of neural cell in spinal column due to mutation in chromosome 5 SMN.[11-15] Motor neurons in spinal cord are only regulate voluntary muscles activities including sitting, crawling, walking, controlling the head and neck, and swallowing. Hence, SMA is often considered as an developmental disability associated with progressive severe physical disability only but does not having any significant cognitive dysfunction.[7,16] Presently, diagnosis of SMA is important to ascertain the appropriate classification of this disorder with reported global frequencies of patients death 1 in 10,000 and 1 in 50 of SMA carriers respectively.[17]

SPINAL MUSCULAR DYSTROPHY: SYMPTOMS

SMA symptoms is started to be observed in babies at approximately 7 to 18 months of age, called type 2 SMA, or intermediate SMA followed by type 1 SMA having fasciculation of the tongue with hand tremors as major observed symptoms. Although, respiratory complications are found to be reported constant threat in children with type 2 SMA usually live to young adulthood and many of them live longer.[18] In types 1 to 4 SMA, legs tend to weaken before

arms and usually remain strong enough for basic functions of modern life.[19-21] In SMA, histopathological changes are reported in motor neurons at spinal cord with a observed loss of large anterior horn cells especially in the motor nuclei of cranial nerves V through XII.[22-24] In type 1 to 4 SMA, symptoms are varied from severe to mild, based on how much SMN protein are observed in the motor neurons which is characterized by hypotonia gradually progressed and lead to general paralysis of limbs and trunk including scoliosis (weakening of muscles that support spine flexibility). The electro-mechanical ventilation and feeding tubes was used to assist the breathing and nutrition of test patient and they with type 1 SMA were found to be survive for number of years as compared to patients, those were not supported with these life savior medical.[25-30] Some intermediates types of SMA are not linked to chromosome 5 or SMN deficiency that vary in muscular impairment severity. While most types which are linked to the chromosome 5 SMN affect mostly the proximal muscles and progressively followed to distal muscles disabilities.[31-34]

SPINAL MUSCUALR DYSTROPHY: TYPES AND THEIR CAUSES

The most common form of SMA (types 1-4) is caused by a mutation in the *SMN1* gene on chromosome 5 which leads to a deficiency of a motor neuron protein called *SMN*, a protein necessary for survival of motor neuron. Mutation in an X-chromosome gene called UBE1 is found to be rarely which causes X-linked SMA which is gene carries instructions for ubiquitin-activating enzyme 1, which helps in binding of a molecular tag to proteins led to premature neural-muscular debilitation.[6] Previously, another rare form of SMA, called *SMA-LED* was also reported having gene-in-proximity on chromosome 5, called *SMN2* to prduce SMN protein (Fig 1).[35]

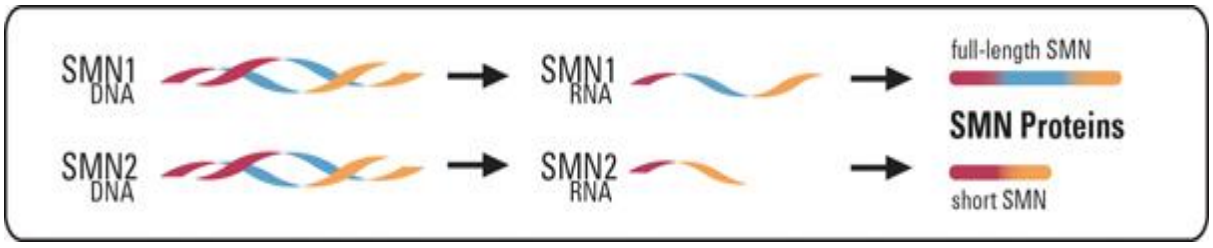

Fig 1: Diagrammatic representation of genetic information followed as per set of instructions of RNA form the SMN1 gene to make full-length SMN protein and from the SMN2 gene to make short SMN protein.

The plastin 3 protein and the ZPR1 protein (zinc finger protein) have been also identified as potential modifiers of SMN-related Spinal muscular atrophy (SMA), which could be become

effective therapeutic agents to be considered for targeted drug therapies used for medical management of SMA.[32-34] SMA is X-linked autosomal genetic inborn disorder and females have two X chromosomes in which one of X chromosome has genetic mutation in SMN considered X-linked disease carriers. However, males have no second X to protect them from lethal effects of a mutated X chromosome showed the ill effects of SMA.[35] SMA was also found reported with mutations in the DYNC1H1 gene on chromosome 14 which is dominantly inherited and sufficient to cause this neuromuscular disorder.[36] SMA was also genetically mapped to identified duplicated region consisting repetitive elements that make it prone to genomic rearrangements and deletions. Thus, two copies of the SMN gene were mapped; survival of Spinal muscular neurons 1 (SMN1) located nearer the end of the chromosome harbour repetitive sequences called telomeric and Survival of Motor Neuron 2 (SMN2) located nearer the centromere called centromeric.[37] Siblings can have lost both copies of SMN1 can have variable SMA phenotypes (very different observable physical or biochemical characteristics) carrying increased copy numbers of SMN2 associated with better functional status of SMA. Apart this, defects in SMN2 initiated modulation of Neuronal Apoptosis Inhibitory protein Gene (NAIP) with varying SMA severity, especially in Type 1 SMA.[4,7,32] So, the diary of the molecular machinery underlying SMA might be proved very helpful for enabling scientists to develop effective therapies.[12-37]

SPINAL MUSCULAR DYSTROPHY: GENETIC ANALYSIS AND COUNSELING

Linkage analysis was done for autosomal recessive SMA where no point mutation was identified SM1 gene or who carry two SMN2 genes.[12] In the contrary, genetic analysis data in Canada was accounted approximately 95% of patients with SMA who have deletions in the SMN1 gene, and about 85% of carriers who have deletions on both copies of SMN1 and those who have a deletion in one copy of SMN2.[14] Prenatal testing for SMA can be performed by chorionic villus sampling (CVS) and amniocentesis to know genetic detection of SMA criteria which is necessary for the implementation of clinical screening program for all neonates that would be able to scrutinized them to get improved start of life and to stay healthy longer to dampen the ill effects of SMA.[38]

SPINAL MUSCULAR ATROPHY: MOLECULAR DIAGNOSTICS TESTS

Previously, PCR-single-strand conformation polymorphism (PCRSSCP) analysis was also used to identified the homozygous absence of SMN1 exon 7 and exon 8.[21,31] Monosomal analysis can also proved needful to perform extensive linkage and dosage analyses to distinguish carriers with two copies of SMN1 (the 2 + 0 SMN1 genotype) from noncarriers (with the normal 1 + 1 genotype) who passed a de novo deletion mutation to an affected child.[32] Using PCRSSCP analysis, Wang and coworkers were also found that 4% of asymptomatic family members of patients with SMA had polymorphisms in SMN1 exon 7 that mimicked the homozygous absence of SMN1.[32] A qualitative PCR-RFLP assay was also used to study the SMN1 deletion assay to detect the homozygous absence of SMN1.[33]

SPINAL MUSCULAR ATROPHY: OTHER EFFECTIVE THERAPEUTIC APPROACHES

Currently no effective treatment or cure is available to treat SMA. However, potential genetically counselled drug therapies may have an active thrust area of investigation and further those new therapeutic approaches will likely to be considered for getting maximum positive and satisfactory medical approaches in the treatment of SMA. These include to collect more detailed information on the pattern of increase full-length mRNA from SMN2 by altering the splicing pattern of SMN2 exon 7 in vivo, either via the activation of transacting factors or by using antisense oligonucleotides; to activate the level of SMN transcription; to stabilize the SMN protein; regeneration of motor neurons by stem cell therapy; and to target modifying potential protein bodies factors other than SMN2 to improve the ill effects of SMA in patients. Now these days, aclarubicin, sodium butyrate and valproic acid have been going to be used as potential pharmaceutical agents which are under advanced research studies to know the increased level of full-length transcripts from SMN2 to be used as promising potential therapeutic agents to treat SMA patients.[39] Adenovirus-vector mediated cardiotrophin-1 gene transfer therapy are still under studies to replace damaged motor neurons in patients of SMA. Hence, further innovative progression on illumination of the molecular genetics and pathogenesis of Spinal muscular atrophy (SMA) should be considered positively to facilitate the therapeutic development for effective treatments and potentially palliative cure for SMA.[40] Biochemical tests were also found to be helpful in progressive muscular dystrophy and neuromuscular diseases like SMA for observing abnormal activities of some of serum metabolic enzymes such as aldolase serum creatine phosphokinase, glutamic oxalacetic transaminase and lactic dehydrogenase.[41] In 2012, an

MDA-supported research team was also reported that a drug called fasudil, which is only approved for research only in the United States, found to be extended the average life span of mice with an SMA-like syndrome from approximately 30 days to more than 300 days. The clinical scientists are believed the drug targeted to muscle impairment might be coined another possible therapeutic avenue for the treatment of SMA.[42]

CONCLUSION

Hence, this informative clinical approach may be proved quite helpful for considerable awareness to understand the knowledge of biochemical basis and genetic analysis interpretation used for Spinal muscular atrophy (SMA) treatment to be known as non-curable genetic disorder. At present, comprehensive qualitative PCR-RFLP is used for SMN gene dosage analysis, linkage analysis and monosomal analysis with advised genetic counselling to get to aware the patients of SMA and their families for approaching its accurate risk assessment, offers the most complete evaluation of SMA patients and their families. So, its early prognosis and diagnosis could have been proved clinical therapeutic approach to treat this disorder followed by rational palliative home care, cost effective diagnostic tests and improving socio-economic ethical dilemma to reduce the ill effects of SMA in patients. Several investigator groups are to be motivated to conduct clinical trials with FDA approved reviewed drug trials and therapeutic treatment to find out trusted positive outcome to get an effective treatment of SMA.

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