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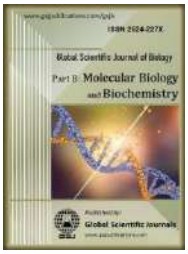

Spinal Muscular Atrophy: A Review

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ABSTRACT

Spinal muscular atrophy (SMA) is a dangerous autosomal recessive disorder in motoneurons associated with muscular weakness and breathing problems. There are numerous studies, metastasis, and reviews focused on the characteristics, pathogenesis, types, severity, diagnosis, and therapy of SMA. The findings of these reports are required to be linked to each other in some aspect. Therefore, this review mentioned the more important fact about SMA. Spinal muscular atrophy (SMA) is an inherited genetic rare neuromuscular disease that occurs due to a mutation in the survival motor neurons 1 (SMN1) gene. SMA1 normal gene responsible for the production of functional survival motor neuron protein with exon7. The mutation of SMN1 led to the production of nonfunctional SMA1protein lacking exon 7. The progeny from both SMA carrier parents yield 25% unaffected, 50% carrier, and 25% affected individuals. The motor neuron protein has crucial role in body bioprocess because this protein regulates muscle contraction by nervous stimuli from the central nervous system. SMA manifests in hypotonia, reduced muscular tone, scoliosis, and inadequate head control, and the more significant one is the weakening of the muscles of the lower limbs, which makes walking difficult. The severity, types, symptoms, and onset time of clinical manifestation depend on the amount and variant of protein produced by other genes called survival motor neurons2 (SMN2). The individual has many copies of SMN2 ranging from one to eight, an increased number of SMN2 gene copies is associated with low severity. In addition to severity, and the type of SMA depending on copies of SMN2, there are five common types of SMA. SMA type 0 associated with one copy of SMA2, is the most severe type lending to death of the embryo before birth; SMA type I associated with two copies of SMA2, is a sever type that occurs during 0-6 months; SMA type II has two to three copies of SMA2, is intermediate variant appears during 6-18 month; SMA type III correlated with three to four copies of SMA2, is mild form onset during 18 month to 18 year; and SMA type IV associated with four or more copies of SMA2, is less sever variant onset after18 year; moreover there is another type of SMA non-related to a mutation in SMN2. The success of SMA therapy, depending early diagnosis, which differs according to SMA severity, age of the affected patient, and availability of medical facilities, however, the diagnosis is determined by clinical evaluation, electromyography (EMG), nerve conduction studies (NCS), muscle biopsy, serum creatine kinase levels (CK), newborn screening, genetic testing. The treatment of SMA mostly depends on gene therapy for example onasemnogene abeparvovec, nusinersen, and risdiplam. More studies are needed to be understanding the basis of SMA pathogenesis and determine the best target of diagnosis and treatment before onset and during the course.

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1. Introduction

SMA is an autosomal recessive inherited illness which is characterized by the progressive loss of both proximal limb and axial muscle tone and strength, resulting in severe disability of the affected motor units. The cause of the disorder is a deletion of the SMN1 gene on the chromosome 5q due to the homozygous or heterozygous deletion along with point mutation of SMN1 gene on the chromosome 5q with a lesser copy of survival motor neuron proteins, which leads to the motor neuron degeneration [1, 2]. SMA has diverse patterns of phenotypical expression and its classification includes five types based on the manifestation age and the maximum motor development attained from less severe SMA type I to the most severe SMA type IV [3].

SMA I patients never learn to sit and present clinically as floppy infants with limited spontaneous movements and paradoxical respiratory patterns before six months of age, without medication, the life expectancy of people suffering from respiratory muscle failure is less than two years [4]. SMA II began six to eighteen months ago and has a milder course. In addition to respiratory involvement 'which usually requires non-invasive breathing before adulthood' and orthopedic difficulties 'such as severe scoliosis and joint contractures', patients can sit but not walk on their own [5].

The mildest forms of SMA are types III and IV, which often have no life-threatening episodes and have a later onset, achievement of independent walking, and a variable clinical outcome [6]. Patients with SMA I and II frequently exhibit dysphagia and failure to grow, necessitating enhanced nutritional absorption by the administration of oral supplements high in protein and calories, or in more severe cases, the implantation of a gastrostomy [7]. A comprehensive approach to rehabilitation is necessary for these patients including respiratory, orthopedic, psychiatric, physiotherapy, speech therapy, and nutritional treatment [8].

2. Epidemiology:

SMA has a carrier frequency of one in 40 to 67 persons and an incidence of one in 11,000 live births which make SMA one of the most common autosomal recessive diseases and the leading cause of morbidity and mortality in children below five years [9]. Epidemiologically, however, numerous research show that SMA III is less common than other forms SMA, although the epidemiologic burden may vary across subtypes. According to Griffiths et al [10], SMA types I, II, and III accounted for 60%, 27% and 12% of all SMA patients respectively.

A recent estimate indicates that the incidence rates of SMA types I, II, and III are around 5.5, 1.9, and 1.7 per 100,000, respectively [11]. SMA arises from the absence of exon 7 in the SMN protein (SMNΔ7) due to alternative splicing and minimal amounts of functional SMN proteins; the key contributors to the clinical heterogeneity in SMA are changes in the copy numbers of the SMN2 paralogous gene. Clinical traits and the amount of SMN2 copies are inversely correlated [12]. Moreover, the SMA severity is related to the time of disease onset during life, approximately 60% of people with SMA experience severe symptoms and pass away in their early years [13].

3. Genetic Analysis of SMA:

Gene conversions or deletions are responsible for the majority of mutations that cause SMA. Due to the presence of two nearly identical copies of SMN1 and SMN2 on chromosome 5, identifying carriers of SMN1 mutations may prove challenging; nonetheless, the principal distinction between SMN1 and SMN2 lies in a solitary nucleotide variation in exon 7, namely T/C conservation [14]. Moreover, exon 7 of the SMN1 mRNA is incorporated, although it is generally omitted in the SMN2 mRNA, which contains T exon 7, as illustrated in Figure 1. Exon 7 is essential for the creation of a stable and fully functional SMN protein [15].

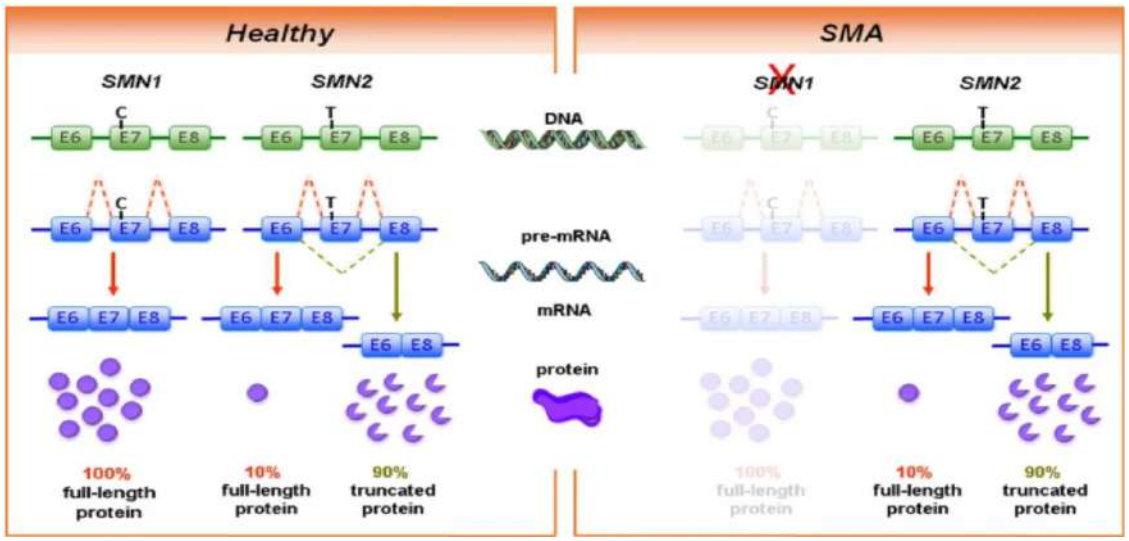

Figure (1): Genetic basis of SMA due to mutations in SMN1 [16].

About one third of 5q-SMA type II patients was observed to harbour a point mutation on one chromosome and a deletion or a gene conversion mutation on the other chromosome [17]. Thus, the SMA diagnostic test will not identify a person possessing this SNP pattern, namely point mutation with a deletion or conversion mutation, as having SMA because there's no single copy of the SMN1 gene [18]. This will make this individual present with SMA symptoms but he/she will be classified as a carrier depending on the quantitative carrier test [19]. SMA patients suffer from the absence of SMN1 exon 7, which is present in homozygous condition in deletion and gene conversional manners [20]. Despite having mutations in SMN1, SMA patients always have at least one normal copy of SMN2 [21]. Although not reported, homozygous deletion of both genes is thought to be fatal [22].

SMN1 deletion on one chromosome and present of two copies on the other have been found in some people, who are known as silent carriers (2 + 0 SMA carrier status) [24]. The individual from two SMA carriers or between an SMA carrier and an SMA-affected individual results in the birth of an SMA-affected kid. Children born to two carrier parents may be affected, carriers, or non-carriers as Figure (2) [25]. Every pregnancy in these households has [26]:

- An SMA-affected child is 25% more likely to be born.
- A 50% risk of having a child who carries the SMA gene.
- There is a 25% possibility of having a child that is not a SMA carrier or has SMA.

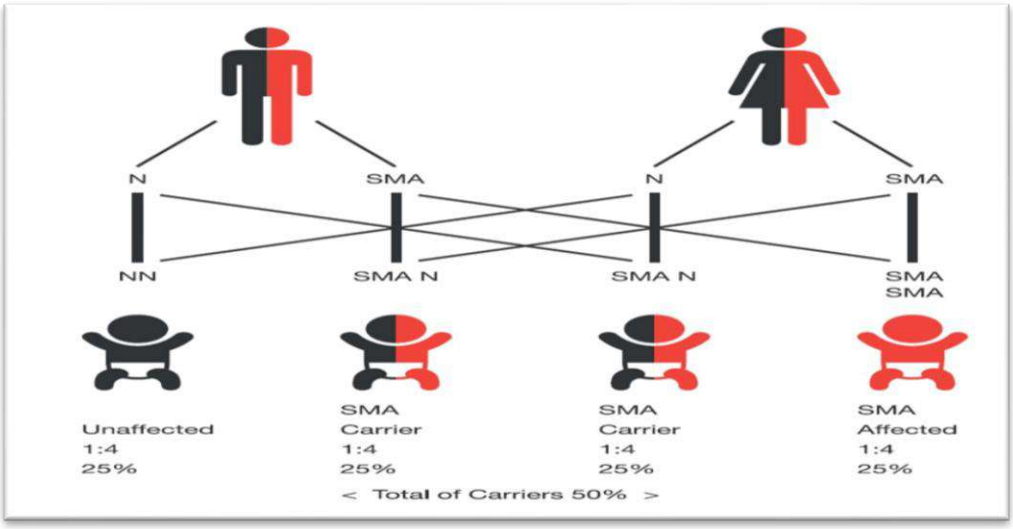

Figure (2): Transmission of the SMN1 gene mutation in SMA [23].

*4. Types of **Spinal Muscular Atrophy:***

SMA is divided into five subtypes, Table (1), according to life expectancy, severity, and age of onset [27]:

4.1. SMA type 0 (congenital SMA):

A fetus affected by this uncommon subtype is impacted prior to birth with decreased movement. Infants with type 0 diabetes usually have respiratory failure and severe muscular weakness at birth, the majority of deaths occur at birth or in the first month of life [28].

4.2. SMA type 1 (severe SMA):

Werdnig-Hoffman disease, or type 1, accounts for about 60% of SMA cases. The first six months of birth are characterized by symptoms such as hypotonia, or reduced muscular tone, and inadequate head control [29]. Breathing and eating difficulties are also experienced by infants with type 1 SMA. Children with type 1 SMA die before turning two years without breathing support [30].

4.3. SMA type 2 (intermediate SMA):

Dubowitz illness, classified as type 2 spinal muscular atrophy (SMA), is characterized by muscle weakness that manifests in children between the ages of 6 and 12 months [31]. Children of this kind can sit independently, although they may require assistance to attain a seated position. Symptoms exhibit considerable variability. The severity and prognosis are contingent upon the age upon diagnosis; whereas some individuals with type 2 SMA may experience premature mortality, many—particularly those diagnosed after 18 months—can survive into adulthood [32].

4.4. SMA type 3 (mild):

Kugelbert-Welander illness, another name for type 3 SMA, is characterized by symptoms that develop after a child has lived for 18 months [33]. Type 3 symptoms include weakening in the muscles of the lower limbs, which makes walking difficult. Breathing problems are rare in people with type 3 MSA, and life expectancy is usually unaffected [34].

4.5. SMA type 4 (adult):

The mildest type of SMA is this one. Usually, it doesn't show up until after the age of 21. Since the signs of muscle weakness develop gradually, most type 4 patients are still ambulatory. Life expectancy is usually unaffected [35].

Table (1): Characteristics of SMA types.

No	Type	MSA2 copies	Severity	Age of clinical symptoms	Affected stage of life	Life expectancy
1	SMA 0	1	most sever	Before birth	prenatal	stillbirth
2	SMA 1	2	sever	0-6 month	infancy	affected
3	SMA 2	2-3	intermediate	6-18 month	Infancy- childhood	affected
4	SMA 3	3-4	mild	18 month -18 year	Childhood-adolescence	unaffected
5	SMA 4	≥ 4	Less sever	Up to 18 year	adulthood	unaffected

5. Molecular Basis of Spinal Muscular Atrophy:

Since SMA is a hereditary disorder, the genes that cause it are inherited from the biological parents. All varieties of spine muscular atrophy are brought on by mutations (alterations) in the SMN1 (survivor motor neuron 1) gene [36]. The severity of the illness varies depending on how many copies of the SMN2 gene patient have [37]. SMN protein is produced by a functional SMN1 gene [38]. This protein is necessary for motor neurons to live and perform their functions. The motor neurons atrophy and eventually die if individual has SMA because body doesn't produce enough of the SMN protein (39). The brain is therefore unable to regulate voluntary motions, particularly those of head, neck, chest, and legs [40]. The SMN2 gene further generates a minor quantity of SMN protein. An individual may possess as many as eight copies of the SMN2 gene [41]. The presence of many copies of the SMN2 gene generally results in milder SMA symptoms, as the additional genes compensate for the absence of the SMN1 protein [42].

6. Diagnosis of Spinal Muscular Atrophy:

6.1. Diagnosis spinal muscular atrophy during pregnancy:

6.1.1. Amniocentesis:

During amniocentesis, the healthcare provider inserts a slender needle into the abdomen to extract a little quantity of amniotic fluid, which is subsequently analyzed by a pathologist for SMA. This examination occurs subsequent to the 14th week of gestation [44].

6.1.2. Chorionic villus sampling (CVS):

A tiny tissue sample is takes from pregnant women placenta through cervix or abdomen, CVS can occur as early as the tenth week of pregnancy [45].

6.2. Diagnostic approaches of spinal muscular atrophy:

The clinical spectrum of SMA can be considered severe early onset to mild adult onset form of the disease. The most common symptoms seen clinically are muscle wasting, flaccidity and hypo tony followed by muscle weakness [46]. It is also important to know that muscles are involved, SMA patients may have abnormal spine curvature, muscle stiffness and contractures, and lung disease [47]. The early detection of these clinical markers thus is important because early intervention can go along way in improving the overall life expectancy and quality of life of such individuals [48]. It is seen in figure 3 that, for the diagnosis of SMA, multiple standard strategies are used for diagnosis.

6.2.1. Clinical evaluation:

A comprehensive early clinical evaluation is essential for diagnosing SMA; the medical professional documents a medical history, conducts a physical assessment, and assesses motor function [50]. An assessment of family

history is crucial to the clinical examination for identifying any documented instances of SMA or related neuromuscular disorders. It is essential to remember that in instances with moderate or atypical symptoms, SMA may not be the primary consideration [50].

6.2.2. Electromyography:

A diagnostic method called electromyography (EMG) is used to evaluate the electrical activity of the muscles and nerves [51]. EMG may show neurogenic alterations in SMA, indicating malfunctioning of the motor neurons. EMG can be used to determine the degree of motor neuron involvement and assist in differentiating SMA from other neuromuscular disorders [52].

6.2.3 Nerve conduction studies:

NCS means tests to assess peripheral nerve activity. The NCS in SMA may be abnormally slightly off or completely normal. These examinations help exclude other neurological disorders and also add the facts that support the SMA diagnosis [53].

6.2.4. Muscle biopsy:

Muscle biopsy can be performed to establish the absence of muscle pathology and rule out disorders such as muscular dystrophy, even if it is not the main diagnostic tool for SMA, the muscle samples in SMA patients usually reveal denervation and atrophy, which confirms the diagnosis [54].

6.2.5. Serum creatine kinase levels:

The serum creatine kinase (CK) measurements can be helpful in distinguishing between muscular dystrophies and SMA, while CK levels in muscular dystrophies are markedly raised, those in SMA are often within the normal range or very slightly higher [55].

6.2.6. Newborn screening:

SMA screening for newborns is one of the important and developing disciplines of the children's protection system, whose aim is to diagnose, treat, and prevent a severe genetic disease. One advantage of the neonatal screening for SMA is the ability to identify affected infants within record time. Newborn screening means that the problem can be detected before it starts showing symptoms; treatment is begun at the beginning, unlike in the past [57].

6.2.7. Genetic testing:

The most reliable method for diagnosing SMA is genetic testing. It offers a conclusive diagnosis, pinpoints the precise genetic mutation, and assists in assessing the illness's severity [58]. Typically, genetic testing entails the following methods: (A) Examining the SMN1 gene is the main genetic test for SMA. The majority of SMA cases are caused by mutations or deletions in this gene, which lower the amounts of SMA protein. This test has a high degree of sensitivity and specificity and can accurately identify SMA [59]. (B) In addition, Information regarding the severity of the disease can be obtained through SMN1 analysis, which counts the number of copies of the SMN2 gene [60]. Patients with SMA who have higher numbers of SMN2 copies usually have milder versions of the disease, whereas patients with lower numbers usually have more severe variants [61].

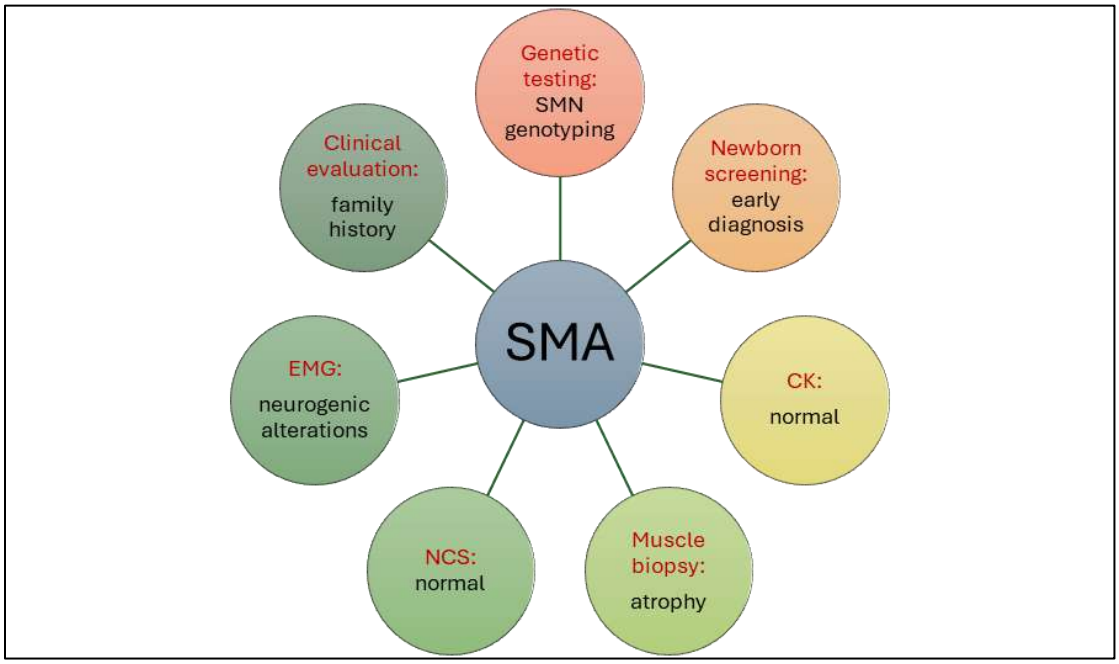

Figure (3): diagram of main approach of SMA diagnosis.

7. Strategies of Spinal Muscular Atrophy Treatment:

7.1. Muscle enhancing therapies:

Reldesemtive, is a selective small-molecule troponin activator for fast-twitch skeletal muscles. Its application in SMA is supported by numerous lines of evidence [62]. This molecule strengthens contraction, sensitizes the sarcomere to calcium effects, and increases troponin C's affinity for calcium [63]. Furthermore, it has been shown that Reldesemtive enhances the human muscular responsiveness to nerve impulses [64].

7.2. Future Prospective in SMN Independent Therapeutic Targets:

Several SMN-independent factors have recently been found to be implicated in the etiology of SMA based on in vitro and in vivo research; as such, they may be potential targets for future therapeutic interventions [65]. The process by which autophagosomes transfer cytoplasmic contents to lysosomes for destruction is known as autophagy [66]. The cytoplasm of SMA motor neurons indicates that deregulation of autophagy could change intracellular trafficking and result in cytotoxicity [67].

The administration of some drugs also lowers apoptotic cell death in the lumbar spinal cord indicating the connection between autophagy and apoptosis in SMA [68]. In the rodents' model, interesting to note that the nuclear factor-kappa B pathway, which has been extensively researched with other pediatric neuromuscular disorders including Duchenne muscular dystrophy, may be involved in SMA pathophysiology [69]. This route is triggered by neurotrophic factors to affect cell survival in mouse spinal cord motor neurons; blockage of this pathway results in a reduction of SMN in SMA motoneurons [70]. Thus, to sum up, these research findings are encouraging, but more proof is required before novel drugs affecting these cellular/molecular pathways can be used in clinical settings [71].

7.3. Gene therapy:

Gene therapy mechanisms available for SMA treatment designed to increase the level of the functional SMN1 protein include Figure (4), Gene Replacement therapy, antisense oligonucleotide therapy, small-molecule modulators, and CRISPR/cas9-based gene editing [72].

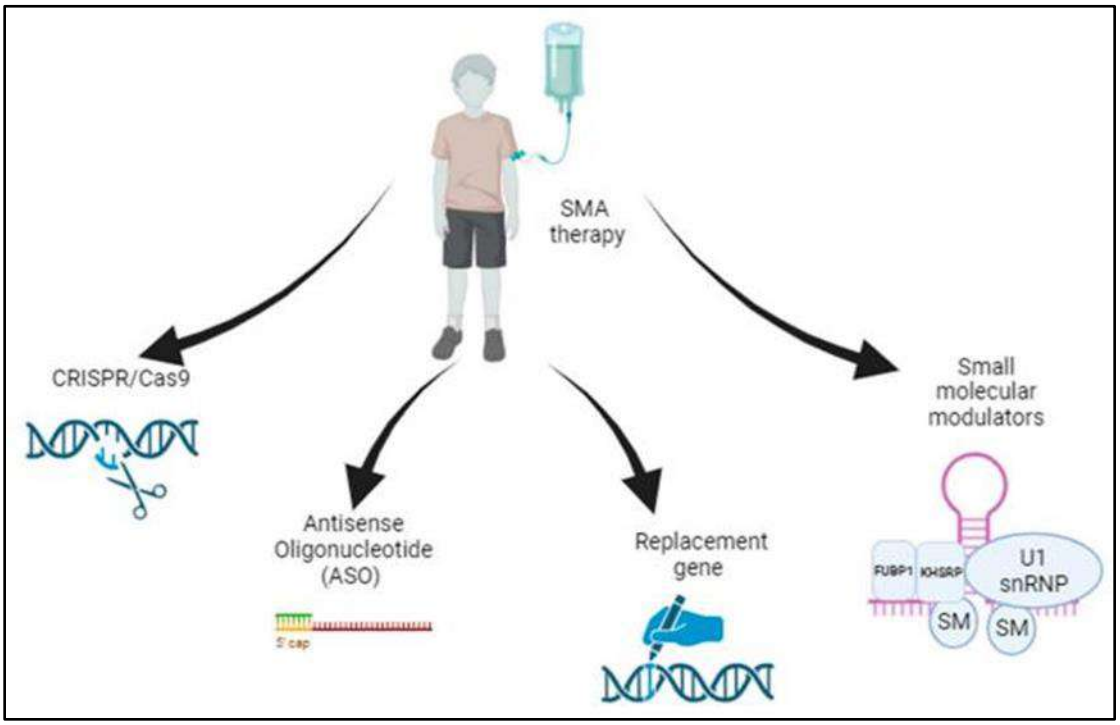

Figure (4): The therapeutic approaches to SMA.

7.4. Response to therapy:

The fact that all of the studies done so far have included patients receiving the advised level of care is probably what has led to the trials' successful outcomes [73]. Additionally, the development of new milestones, improvements in muscle strength, and higher survival rates are drawing attention to newly emerging phenotypes [74]. The availability of trustworthy biomarkers should help us better understand the variety of patient's responses to treatment [75]. Determining prognostic indicators and avoiding long-term exposure to expensive drugs with unidentified long-term negative effects are two uses for this information [76].

Currently, a wide range of biomarkers, including genetic, proteomic, electrophysiological, and imaging methods, are being studied, which include Muscle-specific miRNAs (myomas) are neurofilaments (NFs) [77]. While not yet established as biomarkers, NFs and CSF proteomic profiles have garnered interest as potential SMA approaches [78]. NFs serve as markers for axon degeneration. When infants with SMA type I received nusinersen medication, their clinical condition improved at the same time that the level of CSF NFs in their blood was significantly elevated than in controls [79]. In older patients with milder forms of SMA, comparable findings were confirmed in plasma in another study; the function of NFs remains unsubstantiated, perhaps due to the disease's slower progression [80].

The SMN protein controls the production and RNA metabolism of microRNA (miRNA), a gene expression modulator associated with several neuromuscular diseases. Nusinersen-treated SMA type II and III patients have recently been demonstrated to have reduced expression levels of circulating myomiRs, including 'miR-133a, miR-133b, miR-206, and miR-1' [81]. A recent study assessed the non-targeted CSF proteome patterns in patients with SMA type II and III using mass spectrometry [82]. The investigation identified two groups that differed in age and protein expression linked to neurodegeneration and neuroregeneration. Furthermore, in patients who responded to nusinersen treatment, there was a link with an improvement in motor function [83].

8. Conclusion:

According to the literature, and despite of rare prevalence, there are many variants of SMA, not depending on the mutant gene (SMN1), but because of repeated sequences of another gene

(SMN2), so that the severity, latent period, and life expectancy are independent of affected SMN1 gene but dependent on analogous SMN2 gene, therefor designing and purpose of therapy could be based on SMN1 and/or SMN2. However, the inheritance of disease is related to the SMN1 genotype but the phenotype (severity and onset time) of SMA is linked to SMN1 and SMN2 genotypes.

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