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SPINAL MUSCULAR ATROPHY AS A MOLECULAR-NEUROLOGICAL DISORDER. SMN1 DYSFUNCTION, MOTOR NEURON DEGENERATION AND THE CLINICAL VALUE OF EARLY DIAGNOSIS

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Abstract. Spinal muscular atrophy is a genetically determined neuromuscular disease in which dysfunction of the SMN1 gene causes a systemic deficiency of survival motor neuron protein and selective vulnerability of lower motor neurons. Although the molecular defect is present in all nucleated cells, the most clinically important consequences occur in the anterior horn cells of the spinal cord and in the neuromuscular junction. This review article analyzes the relationship between SMN1 loss, altered SMN2 splicing, RNA-processing defects, axonal transport failure, synaptic instability, and progressive muscle denervation in a structured IMRAD format. The literature review emphasizes that the introduction of nusinersen, onasemnogene abeparvovec and risdiplam has changed the natural history of the disease, but therapeutic benefit remains strongly dependent on the number of viable motor neurons at the time of treatment. Therefore, newborn screening and presymptomatic diagnosis are presented as central clinical strategies rather than optional diagnostic additions. The article also discusses current limitations of disease-modifying therapy, including incomplete recovery in advanced disease, the need for long-term safety monitoring, economic barriers and unequal access to screening. The findings support an integrated molecular-clinical approach in which genetic confirmation, early referral, multidisciplinary care and timely treatment are combined to reduce irreversible neurological disability.

Keywords: spinal muscular atrophy, SMN1 gene, SMN2 gene, SMN protein, motor neuron degeneration, gene therapy, newborn screening, neuromuscular disease

SPINAL MUSHAK ATROFIYASI MOLEKULYAR-NEVROLOGIK KASALLIK SIFATIDA. SMN1 GENI DISFUNKSIYASI, MOTOR NEYRONLAR DEGENERATSIYASI VA ERTA TASHXISNING KLINIK AHAMIYATI

Annotatsiya. Ushbu maqolada spinal mushak atrofiyasi SMN1 genining disfunksiyasi bilan bog‘liq irsiy neyromushak kasalligi sifatida tahlil qilinadi. SMN oqsili yetishmovchiligi pre-mRNK splaysingi, aksonal transport, sitoskelet barqarorligi va nerv-mushak birikmasi faoliyatiga ta’sir ko‘rsatib, orqa miyaning oldingi shoxlaridagi pastki motor neyronlarning bosqichma-bosqich degeneratsiyasiga olib keladi. Maqola IMRAD talablari asosida qayta tuzildi va SMN1 geni yo‘qolishi, SMN2 genining kompensator imkoniyati, motor neyronlarning selektiv zaifligi, kasallikning klinik fenotiplari hamda zamonaviy kasallik-modifikatsiyalovchi davolash usullari o‘rtasidagi bog‘liqlik yoritildi. Tahlil natijalari shuni ko‘rsatadiki, davolash samaradorligi simptomlar paydo bo‘lishidan oldin tashxis qo‘yilgan bolalarda eng yuqori bo‘ladi. Shu sababli yangi tug‘ilgan chaqaloqlar skriningi, erta genetik tasdiqlash, multidisiplinar kuzatuv va davolashni o‘z vaqtida boshlash spinal mushak atrofiyasida uzoq muddatli nevrologik natijalarni yaxshilashning asosiy yo‘nalishlari hisoblanadi.

Kalit so‘zlar: spinal mushak atrofiyasi, SMN1 geni, SMN2 geni, SMN oqsili, motor neyron degeneratsiyasi, gen terapiyasi, neonatal skrining, neyromushak kasalligi

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СПИНАЛЬНАЯ МЫШЕЧНАЯ АТРОФИЯ КАК МОЛЕКУЛЯРНО-НЕВРОЛОГИЧЕСКОЕ ЗАБОЛЕВАНИЕ. ДИСФУНКЦИЯ ГЕНА SMN1, ДЕГЕНЕРАЦИЯ МОТОНЕЙРОНОВ И КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ РАННЕЙ ДИАГНОСТИКИ

Аннотация. В статье спинальная мышечная атрофия рассматривается как наследственное нейромышечное заболевание, связанное с дисфункцией гена SMN1 и дефицитом белка выживания мотонейронов. Недостаточность SMN нарушает сплайсинг пре-мРНК, аксональный транспорт, стабильность цитоскелета и функцию нервно-мышечного соединения, что приводит к прогрессирующей дегенерации нижних мотонейронов передних рогов спинного мозга. Материал переработан в соответствии со структурой IMRAD, а также дополнен обзором литературы, отражающим связь между молекулярным дефектом, клиническими фенотипами, современной терапией и значением ранней диагностики. Особое внимание уделено тому, что максимальная эффективность нусинерсена, онасемногена абепарвовека и рисдиплама достигается при назначении лечения до развития выраженной денервации. Подчеркивается клиническая значимость скрининга новорожденных, своевременного генетического подтверждения диагноза, мультидисциплинарного наблюдения и равного доступа к инновационной терапии.

Ключевые слова: спинальная мышечная атрофия, ген SMN1, ген SMN2, белок SMN, дегенерация мотонейронов, генная терапия, неонатальный скрининг, нейромышечное заболевание

INTRODUCTION

Spinal muscular atrophy is one of the most clinically significant inherited neuromuscular diseases because a single genetic defect can lead to early motor disability, respiratory insufficiency and, in severe cases, infant mortality. The disease is characterized by progressive weakness of skeletal muscles as a result of lower motor neuron degeneration in the anterior horns of the spinal cord. In clinical practice, the disorder is not limited to muscle weakness alone. It affects feeding, coughing, ventilation, posture, motor development and quality of life, which makes timely recognition essential for pediatricians, neurologists, geneticists and rehabilitation specialists [3, 4, 8].

The central molecular event in spinal muscular atrophy is functional loss of the survival motor neuron 1 gene located on chromosome 5q13. The discovery and characterization of this gene created the basis for modern molecular diagnosis and for therapies aimed at increasing the level of functional SMN protein [1]. A paralogous gene, SMN2, is present in humans and partially compensates for SMN1 loss. However, because most SMN2 transcripts exclude exon 7, only a small proportion of full-length stable SMN protein is produced. This molecular peculiarity explains both the severity of the disease and the possibility of therapeutic intervention through splicing modification [2, 7, 15].

The clinical landscape of spinal muscular atrophy has changed profoundly over the last decade. Before disease-modifying therapy became available, management was primarily supportive and focused on respiratory care, nutrition, orthopedic prevention and rehabilitation. The approval and introduction of nusinersen, onasemnogene abeparvovec and risdiplam shifted treatment from symptomatic support to molecularly targeted intervention [9, 10, 11, 12, 13]. Nevertheless, the biological window for optimal benefit is narrow. Once motor neurons are lost, current therapies cannot fully restore the original neuronal pool. For this reason, early genetic diagnosis and newborn screening are now considered major determinants of long-term outcome [18, 19, 20, 24].

LITERATURE REVIEW

The literature describes spinal muscular atrophy as a disease in which molecular genetics, neurobiology and clinical medicine are inseparably connected. Early genetic studies demonstrated that homozygous deletion or functional impairment of SMN1 is the main cause of the 5q-associated form of the disease [1]. Subsequent work clarified that SMN protein is required for small nuclear ribonucleoprotein assembly and pre-mRNA splicing, but also participates in axonal growth, cytoskeletal organization and synaptic stability. These findings explain why a ubiquitous protein deficiency produces particularly severe consequences in motor neurons, which have long axons, high metabolic demands and dependence on efficient intracellular transport [2, 7].

Clinical reviews and consensus recommendations emphasize that the phenotype of spinal muscular atrophy is broad. Severe infantile-onset disease is associated with profound hypotonia, impaired swallowing and respiratory insufficiency, while later-onset forms may present with delayed motor milestones, proximal weakness, scoliosis and loss of ambulation over time. SMN2 copy number is an important modifier of severity, although it is not an absolute predictor for every individual patient [3, 4, 6, 8]. This variability requires clinicians to interpret molecular results together with the age of onset, motor function, respiratory status and family history.

Therapeutic literature shows a consistent principle across different treatment modalities. The earlier functional SMN levels are restored, the better the expected motor outcome. Nusinersen improves SMN2 exon 7 inclusion through an antisense oligonucleotide mechanism and has demonstrated benefit in infantile and later-onset disease [9, 10]. Onasemnogene abeparvovec introduces a functional copy of SMN1 through gene replacement therapy and has produced major survival and motor benefits in early-treated children [11, 21]. Risdiplam is an oral SMN2 splicing modifier with evidence of efficacy across several clinical types [12, 13]. Adult studies and real-world cohorts confirm benefit beyond infancy, but also show that advanced denervation limits the degree of recovery [14, 22].

Newborn screening has become one of the most important public health topics in spinal muscular atrophy. Population-based screening generally detects absence of SMN1 exon 7 and allows referral before symptoms become clinically evident. Published screening programs and treatment algorithms support rapid confirmation of the diagnosis, assessment of SMN2 copy number and early selection of therapy [18, 19, 20]. Long-term observations from presymptomatically treated infants indicate that early intervention can substantially improve motor development, reduce respiratory complications and change expected survival patterns [24].

MATERIALS AND METHODS

This article was prepared as a narrative scientific review based on peer-reviewed literature dealing with the molecular genetics, pathogenesis, clinical course, diagnosis and treatment of spinal muscular atrophy. The review focused on the role of SMN1 dysfunction, SMN protein deficiency, degeneration of lower motor neurons, the therapeutic importance of SMN restoration and the need for newborn screening. These themes were organized into an IMRAD structure to present a coherent molecular-clinical interpretation of the disease.

The literature synthesis prioritized international review papers, consensus recommendations, randomized clinical trials, gene therapy studies, newborn screening reports, real-world observational research and papers addressing safety, quality of life and health-economic aspects. Data were interpreted qualitatively rather than statistically because the aim was not to perform a systematic meta-analysis. The main analytical approach was to connect molecular mechanisms with clinical consequences and practical management decisions. Citations in the text are presented with

numbers in square brackets, and the reference list is formatted in APA style according to the same numbering sequence.

RESULTS

The analysis identified four major interconnected findings. First, SMN1 dysfunction is the primary molecular cause of 5q-associated spinal muscular atrophy, while SMN2 copy number modifies but does not eliminate the disease risk. Second, SMN protein deficiency affects several cellular processes at the same time, including RNA processing, axonal transport, mitochondrial stability, cytoskeletal dynamics and neuromuscular junction maturation. Third, lower motor neurons are selectively vulnerable because their long axonal structure and continuous synaptic demands make them highly dependent on efficient intracellular maintenance. Fourth, clinical benefit from modern therapy is strongly time-dependent because preservation of motor neurons before irreversible degeneration is more achievable than recovery after substantial neuronal loss [2, 7, 15].

At the molecular level, the absence or severe impairment of SMN1 leads to insufficient production of full-length SMN protein. SMN2 cannot fully compensate because exon 7 is excluded from most transcripts, resulting in truncated unstable protein. This defect creates a persistent gap between the amount of SMN protein required for normal motor neuron function and the amount actually available in affected patients. The consequence is not a single isolated biochemical abnormality but a cascade of cellular vulnerability involving ribonucleoprotein assembly, mRNA metabolism, local axonal translation, synaptic function and stress resistance [1, 2, 7].

The degeneration of motor neurons begins before many clinical signs are recognized. Loss of motor neuron function leads to reduced trophic signaling at the neuromuscular junction, followed by muscle fiber denervation and atrophy. In severe infantile forms, this process explains early hypotonia, poor antigravity movements, weak cry, feeding difficulty and respiratory insufficiency. In milder forms, the same pathogenic chain progresses more slowly and may present as delayed walking, frequent falls, proximal weakness, scoliosis and reduced endurance. The presence of more SMN2 copies may reduce severity, but the disease remains biologically active when SMN levels are inadequate [3, 4, 8].

Disease-modifying therapies share the common purpose of increasing functional SMN protein. Nusinersen and risdiplam act mainly through SMN2 splicing modification, whereas onasemnogene abeparvovec provides a functional SMN1 transgene. These approaches differ in route of administration, monitoring requirements and long-term safety considerations, but they converge on the same therapeutic target. The available evidence indicates that treatment produces the greatest benefit when initiated before symptoms or at the earliest possible clinical stage [9, 10, 11, 12, 13, 14].

Newborn screening changes the diagnostic sequence by identifying affected infants before motor neuron loss becomes clinically advanced. This creates the opportunity to confirm the diagnosis, evaluate SMN2 copy number, counsel the family and start treatment while motor neurons are still preserved. The most important practical implication is that screening should be linked to a rapid treatment pathway. A screening program without timely confirmatory testing and therapeutic access cannot fully achieve its clinical purpose [18, 19, 20, 24].

Table 1. Molecular and clinical links in spinal muscular atrophy

Biological level	Main disturbance	Clinical consequence
Genetic level	Loss of functional SMN1 with incomplete compensation by SMN2.	Variable SMA phenotype modified by SMN2 copy number.

RNA-processing level	Defective snRNP assembly and altered pre-mRNA splicing.	Reduced capacity of motor neurons to maintain normal cellular function.
Axonal and synaptic level	Disrupted axonal transport, cytoskeletal instability and neuromuscular junction immaturity.	Progressive denervation, proximal weakness and loss of motor milestones.
Therapeutic level	SMN restoration through splicing modification or gene replacement.	Greatest benefit when treatment starts before irreversible motor neuron loss.

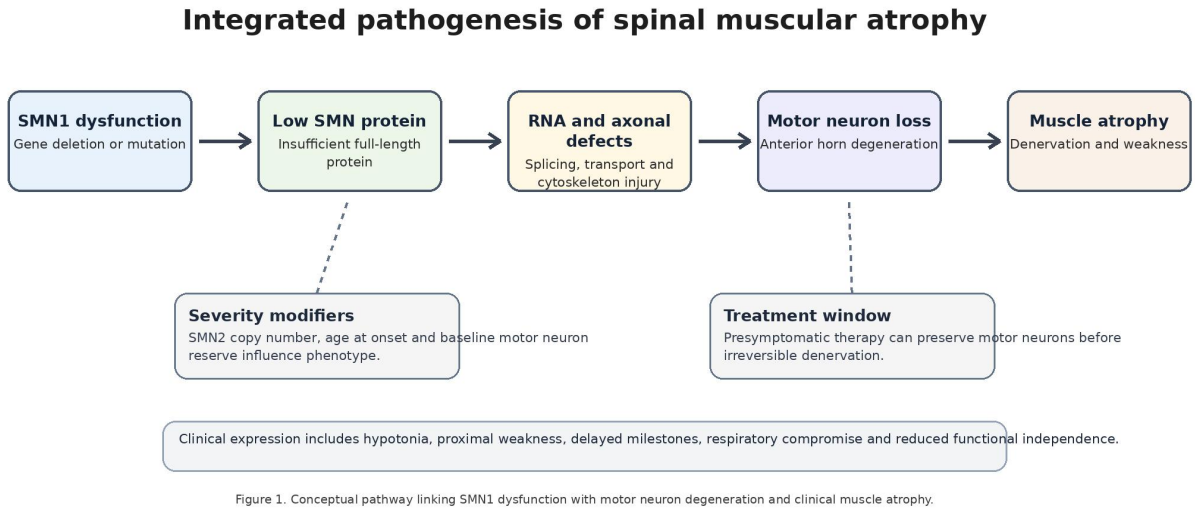


Figure 1. Conceptual pathway linking SMN1 dysfunction with motor neuron degeneration and clinical muscle atrophy.

Figure 1. Integrated molecular pathway from SMN1 dysfunction to motor neuron degeneration and muscle atrophy.

Table 2. Disease-modifying therapeutic strategies in spinal muscular atrophy

Therapeutic approach	Main target	Key advantage	Important limitation
Nusinersen	SMN2 splicing modification.	Evidence in infantile and later-onset SMA.	Requires repeated intrathecal administration.
Onasemnogene abeparvovec	Delivery of a functional SMN1 transgene.	Potential one-time systemic gene replacement.	Requires immune and hepatic safety monitoring.
Risdiplam	Oral SMN2 splicing modification.	Convenient systemic administration.	Long-term surveillance remains necessary.
Multidisciplinary care	Respiratory, nutritional, orthopedic and rehabilitation support.	Improves survival, function and quality of life.	Cannot replace early molecular therapy.

DISCUSSION

The reviewed evidence supports the view that spinal muscular atrophy should be understood as a molecular-neurological disease with systemic implications. The genetic defect is well defined, but the clinical outcome is shaped by the timing of diagnosis, the amount of remaining motor neuron reserve, the availability of therapy and the quality of multidisciplinary care. This explains why two patients with similar genetic findings may experience different functional trajectories. Molecular confirmation is essential, but it should not replace careful clinical assessment and longitudinal monitoring [3, 4, 17].

The selective vulnerability of motor neurons remains a key biological question. SMN protein is expressed in many tissues, yet lower motor neurons are among the first and most severely affected cells. Their long axons require efficient transport of mRNA, proteins, mitochondria and vesicles. The neuromuscular junction also requires continuous structural maintenance and activity-dependent adaptation. When SMN levels are low, these demands cannot be fully met, and the motor unit becomes progressively unstable. This interpretation is consistent with molecular and neurobiological studies showing abnormalities in RNA metabolism, axonal transport and synaptic integrity [2, 7, 15].

Modern treatment has transformed spinal muscular atrophy, but it has not removed all clinical challenges. Children treated after symptom onset may improve, stabilize or gain motor skills, but the degree of recovery is limited by the extent of pre-existing denervation. Adults may also benefit from therapy, although outcomes often focus on stabilization, endurance, upper limb function and quality of life rather than complete reversal of disability [14, 23]. These realities should be communicated clearly to families so that expectations are realistic and rehabilitation remains an active part of care.

Safety monitoring is another important issue. Antisense oligonucleotide therapy requires repeated intrathecal administration and clinical surveillance. Gene replacement therapy may be associated with immune-mediated and hepatic adverse effects, which require appropriate laboratory monitoring and management. Oral splicing modification improves convenience but still requires long-term follow-up. As treated cohorts age, registries and real-world studies will be necessary to understand durability of response, late adverse effects and optimal sequencing or combination of therapies [21, 22, 26].

The economic and ethical dimensions of spinal muscular atrophy are increasingly important. The cost of therapy, the infrastructure required for newborn screening and differences in access between countries create unequal outcomes. Health-economic analyses suggest that early diagnosis and treatment can reduce long-term burden, but the initial cost remains a major barrier in many health systems [25]. From an ethical perspective, the availability of highly effective early treatment strengthens the argument for newborn screening, because delayed diagnosis may mean preventable neurological loss.

For countries developing or expanding genetic screening, the experience from established programs suggests a staged strategy. Screening should be accompanied by confirmatory molecular testing, genetic counseling, referral to specialized neuromuscular centers, standardized treatment algorithms and long-term outcome registries. Such integration is crucial because spinal muscular atrophy progresses rapidly in infancy and administrative delays can reduce the benefit of therapy. The clinical goal is not simply to diagnose SMA but to diagnose it early enough for treatment to preserve meaningful motor function [18, 19, 20, 24].

CONCLUSION

Spinal muscular atrophy is a severe inherited neuromuscular disorder in which SMN1 gene dysfunction causes SMN protein deficiency and initiates a cascade of molecular, cellular and

clinical consequences. The most important pathological outcome is progressive degeneration of lower motor neurons, leading to muscle denervation, weakness, respiratory complications and disability. The SMN2 gene modifies severity but cannot reliably compensate for the loss of SMN1.

The main scientific and clinical lesson from recent advances is that the timing of intervention determines the size of benefit. Disease-modifying therapies can alter the natural history of spinal muscular atrophy, but their best results are achieved when treatment begins before irreversible motor neuron loss. Therefore, newborn screening, rapid genetic confirmation, early multidisciplinary referral and equitable access to therapy should be regarded as central components of modern SMA care. Future research should focus on long-term safety, biomarkers of treatment response, optimized therapeutic combinations and strategies that make early diagnosis and treatment accessible to all affected children.

DECLARATIONS

No new human or animal data were generated for this review article. Ethical approval and informed consent were not required because the article is based on previously published literature. The authors should complete the author contribution section according to the actual role of each participant before journal submission. The authors declare that there is no conflict of interest. No specific external funding was received for the preparation of this manuscript.

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