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Invited Review

Spinal Muscular Atrophy Types, Innovations in Diagnosis and Treatment

Spinal Musküler Atrofi Tipleri, Tanı ve Tedavide Yenilikler

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ABSTRACT

Spinal muscular atrophy (SMA) is a severe condition with recent advancements in diagnosis and treatment. Its prevalence might be higher than anticipated in countries, where consanguineous marriages are common, implying that there could be cases of prenatal deaths. It is crucial for pediatricians to be familiar with the various forms of SMA that exhibit different symptoms and to promptly refer patients to pediatric neurology to ensure timely treatment and prevent complications. Without treatment, decreased levels of survival motor neuron (SMN) protein can result in disability and even death, ranging from functional motor impairments to muscle weakness and respiratory failure. Clinically, the severity of SMA varies significantly depending on the loss of lower motor neurons, ranging from prenatal forms to adult-onset forms, leading to progressive muscle weakness and atrophy. Homozygous deletion of the *SMN1* gene is responsible for approximately 95-98% of SMA cases. A *SMN2* gene closely related to SMA can partially compensate for the loss of *SMN1*, with disease severity correlating with the number of copies. For patients who cannot receive intrathecal treatment with nusinersen, due to spinal deformities like advanced scoliosis, risdiplam may serve as an alternative treatment option. We eagerly await the publication of long-term results of the studies for patients who have received multiple treatments in some way. Future research will potentially identify more cost-effective and easily measurable biomarkers. It is crucial to enhance pediatricians' awareness of this disease, as early treatment can yield promising outcomes.

Keywords: Spinal muscular atrophy, treatment, biomarker, innovation

ÖZ

Spinal musküler atrofi (SMA) son zamanlarda tanı ve tedavisinde gelişmeler olan ciddi bir hastalıktır. Akraba evliliklerinin yüksek olduğu ülkelerde taşıyıcılarının sık olması, bazı tiplerinde prenatal eksitus olan hastalar olduğu için gerçek insidans ve prevelansının tahmin edilenden daha yüksek olabileceğini düşündürmektedir. Pediatri doktorları tarafından bu hastalığın farklı görünümleri olan tiplerini iyi bilmeleri ve zamanında çocuk nörolojisine yönlendirmeleri hastaların komplikasyonlar gelişmeden tedavi şansını kaçırmamaları açısından önemlidir. Klinik olarak alt motor nöronların kaybına bağlı olarak şiddeti prenatal formdan erişkin başlangıçlı forma kadar oldukça değişken olup progresif kas güçsüzlüğü ve atrofi gelişir. Eğer tedavi edilmezse hayatta kalma motor nöron geni (SMN) protein düzeyindeki azalma fonksiyonel motor defisitlerden, kas güçsüzlüğü, solunum yetersizliğine kadar değişebilen sakatlık ve ölüme yol açabilir. *SMN1* geninin homozigot silinmesi, SMA hastalarının yaklaşık %95-98'ini oluşturur. Homolog bir *SMN2*, *SMN1* silinmesini kısmen telafi edebilir ve kopya sayısı, hastalığın ciddiyeti ile ilişkilidir. Nusinersen tedavisini alamayan (ileri skolyoz gibi nedenlerle) hastalar için risdiplam bir başka tedavi seçeneği olabilir. Bir şeklide çoklu tedavi alan hastaların uzun süreli sonuçlarının yayınlanmasını merakla beklemekteyiz. İleride yapılacak çalışmalar daha ucuz ve kolay ölçülebilen biomarkerların belirlenmesine olanak sağlayabilir. Pediatristlerin erken tedavisiyle yüz güldürücü sonuçlar alınabilen bu hastalık hakkında farkındalığını artırmak gerektiğini düşünmekteyiz.

Anahtar kelimeler: Spinal musküler atrofi, tedavi, biyomarker, yenilik

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder, and formation of its most common form, 5q SMA, results from biallelic mutations in the *survival motor neuron-1 (SMN)* gene. However, there are various genetic subtypes of SMA. In the majority of cases (95%), homozygous deletions of the *SMN1* gene, which encodes the vital SMN protein essential for motor neuron survival induces development of SMA[1]. Less frequently, it can arise from missense, frameshift, or heterozygous mutations in one allele paired with point mutations in the other allele[2]. SMA types stemming from mutations in genes other than 5q are referred to as non-5q SMAs. Its reported incidence ranges from 1:6,000 to 1:30,000[3]. Clinically, the loss of lower motor neurons leads to progressive muscle weakness and atrophy, with disease severity varying widely, from prenatal onset to adult-onset forms.

Both *SMN1* and *SMN2* genes encode the SMN protein, but while *SMN1* generates a fully functional protein, only 10% of the protein produced by *SMN2* is functional[4]. This difference arises from a mutation in intron 7 of the *SMN2* gene. As a neurodegenerative disorder, decreased expression of SMN gene and progressive degeneration of motor neurons in the spinal cord and brainstem are characteristic features of SMA[5]. The level of SMN protein produced by *SMN2* copies, when *SMN1* gene is rendered completely functionless, is inversely related to the severity of SMA. The severity and course of the disease range from mild (type 4) to severe (type 1) type depending on the variable number of less stable *SMN2* gene copies[6]. The *SMN2* copy number serves as the primary, though not exclusive, prognostic indicator for SMA types. In SMA type 1, 86% of patients have 2 copies of the *SMN2* gene, 87% of SMA type 2 have 3 copies, 64% of type 3 individuals have 3 copies, and 31% have 4 copies[7].

Types of Spinal Muscular Atrophy

If left untreated, the reduction in SMN protein levels can result in varying degrees of disability and even death, encompassing functional motor impairments, muscle weakness, and respiratory failure[8]. Historically, SMA has been categorized into different types (types 0-4) based on disease severity and the timing of clinical symptoms.

In SMA type 0, symptoms manifest in utero, and there are noticeable signs of profound muscle weakness at birth. SMA type 1, is the most prevalent form that manifests symptoms within the first 6 months of life, and affected individuals are unable to sit independently. Type 2 SMA typically begins to show symptoms after the first 6 months of life, and patients can sit but cannot walk without assistance. Patients with type 3 can initially walk, but they gradually lose their ability to walk with disease progression. In cases where symptoms emerge before the age of 3 (type 3a), roughly half of the individuals lose their ability to walk before reaching adulthood. For type 3b, symptoms appear after 3 years of age, and some individuals can maintain their ability to walk even beyond the age of 40. In the adult-onset type 4 SMA, patients do not lose their ability to walk[9].

In SMA patients, kyphosis, a forward curvature of the spine, typically develops before the age of three, which may later progress to scoliosis or kyphoscoliosis, a combination of forward and lateral spinal curvatures[10]. Consequently, comprehensive patient monitoring, especially for those receiving high-cost medications for the treatment of SMA, and early intervention for spinal deformities through assessments of two-plane radiographic series are crucial for achieving better functional outcomes and prolonged survival.

Treatment of Spinal Muscular Atrophy

Since 2016, the United States Food and Drug Administration has granted approval for three disease-modifying therapies for the treatment of SMA, all of which show their effects by elevating SMN protein levels[11].

Nusinersen (SPINRAZA®), initially marketed as an intrathecal formulation, and recently available in an oral form known as risdiplam (Evrysdi®)[12] are effective through distinct mechanisms to boost *SMN2* mRNA, thus increasing the production of fully functional SMN protein. These therapies are approved for use in pediatric patients, neonates, and adults.

Onasemnogene abeparvovec (ZOLGENSMA®) represents a gene replacement therapy targeting the *SMN1* gene. This therapy involves intravenous administration of an adeno-associated virus 9 (AAV9) and is approved for children under two years of age[13]. Gene therapy, while costly and therefore limited in its indications, entails a one-time injection. It facilitates the transfer of the *SMN1* gene, delivered by the AAV9 vector, through the blood-brain barrier and into motor neuron cells within the central nervous system. Presently, gene therapy is indicated for patients with the diagnosis of 5qSMA type 1 resulting from biallelic *SMN1* gene

mutations and for patients under the age of 2 with a maximum of four copies of the *SMN2* gene[14].

All three drugs have undergone numerous tests in presymptomatic patients younger than 42 days of age. All patients with three copies of the *SMN2* gene achieved independent ambulation before reaching 2 years of age. Half of the patients carrying 2 copies of the *SMN2* gene displayed normal motor development, while the other half experienced mild to moderate developmental delays[15]. These findings underscore the critical importance of early diagnosis and prompt initiation of treatment, particularly for SMA patients carrying two copies of *SMN2* gene[16].

Biomarkers

Responses to nusinersen, onasemnogene abeparvovec, and risdiplam treatments exhibit significant variations among individuals influenced by multiple factors, including *SMN2* copy number, age at the start of treatment, and disease severity[17-21]. Due to this inherent variability, there is an urgent need for SMA biomarkers aiding in treatment decisions, and in the prediction of prognosis (prognostic biomarkers) and treatment outcomes (predictive biomarkers)[22]. Moreover, numerous clinical trials are in progress, focusing on approaches beyond targeting the SMN protein, such as reversing motor neuron loss, enhancing motor function, neuromuscular junction improvement, or enhancing muscle performance[23,24]. Combining SMN-dependent and independent therapeutic modalities may prove to be the most effective strategy for the treatment of SMA[25]. Consequently, the development of novel prognostic, predictive, and pharmacodynamic biomarkers serving as valuable outcome measures in clinical trials and for monitoring responses to evolving treatment regimens over time conveys utmost importance[26,27].

While SMA mRNA and protein levels naturally serve as biomarkers for SMA, their levels in the bloodstream, and central nervous system do not correlate with CNS levels. Recently, extravesicular blood samples obtained from SMA type 2 patients have revealed the presence of full-length SMN transcripts. Additionally, nusinersen treatment has been associated with decreased neurofilament (NF) and SMN transcript levels[28]. Other potential biomarkers encompass genetic factors like *SMN2* copy number, *SMN2* polymorphisms, genetic regulators, transcription and splicing regulators, microRNAs, methylation factors, long non-coding RNAs, NF, tau protein, magnetic resonance imaging, muscle imaging techniques, and electrophysiological parameters, including compound muscle action potential amplitude, motor unit number estimation methodologies, and repetitive nerve stimulation[29-32].

Newborn Screening Programs

The implementation of newborn screening (NBS) for SMA has brought about a profound transformation in the outlook for diagnosed patients. Real-world studies have illuminated the fact that only 34% of individuals possessing 3, 4, or 5 copies of *SMN2* were able to achieve the ability of independent walking[33]. Those who started to receive treatment after the onset of symptoms had notably lower chances of regaining their ambulatory abilities[34]. As implementation of NBS has became widespread, substantial real-world data on the efficacy of early SMA treatment have emerged. A systematic review of the findings of 18 studies by Aragon-Gawinska et al.[35] revealed that early treatment outcomes were contingent upon both the *SMN2* copy number and the initial neurological presentation of the patients. Regrettably, there is no foolproof method to detect early-stage SMA symptoms. In the absence of a positive NBS result, pediatricians may struggle to identify subtle abnormalities unless they possess expertise in the diagnosis of SMA. Functional motor outcome assessment tools like Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders can facilitate symptom measurement and making comparisons during monitoring of the treatment. In the future, following the conduction of well-designed clinical trials, noninvasive in-utero diagnostic tests followed by prenatal treatment might become a topic of consideration.

Making treatment decisions for patients with 4 *SMN2* copies poses a unique challenge. While adhering to a "wait-and-see" approach is not always straightforward, it has been observed that these patients may exhibit less than four copy numbers in different assessments. More comprehensive data is essential to provide recommendations for these individuals[36,37]. It is critically important to note that current SMA treatments come with substantial costs. Consequently, robust health-related economic analyses are required to assess the value of treating SMA patients identified through NBS programs.

Conclusion

In countries like ours, where consanguinity rates are approximately 30%, early detection of SMA holds immense significance. Identifying high-risk pregnancies for SMA through premarital screening as soon as

possible is also of great economic importance for the nation. Delayed diagnosis and treatment can hinder the achievement of desired favorable outcomes.

Risdiplam could serve as a potential alternative for patients unable to receive nusinersen. This is particularly relevant for cases having advanced scoliosis or other contraindications. We eagerly anticipate the release of long-term results from studies performed with patients who have undergone multiple treatment regimens.

Future research endeavors may pave the way for the discovery of more cost-effective and readily accessible biomarkers. Increasing awareness among pediatricians about this treatable disease is imperative and should be prioritized.

Ethics

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Author Contributions

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REFERENCES

1. Kimizu T, Ida S, Okamoto K, Awano H, Niba ETE, Wijaya YOS, et al. Spinal Muscular Atrophy: Diagnosis, Incidence, and Newborn Screening in Japan. Int J Neonatal Screen. 2021;7(3):45. doi: 10.3390/ijns7030045
2. Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. Brain. 2014;137(11):2879-96. doi: 10.1093/brain/awu169
3. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80(1):155-65. doi: 10.1016/0092-8674(95)90460-3
4. Burnett BG, Muñoz E, Tandon A, Kwon DY, Sumner CJ, Fischbeck KH. Regulation of SMN protein stability. Mol Cell Biol. 2009;29(5):1107-15. doi: 10.1128/MCB.01262-08
5. Chaytow H, Huang YT, Gillingwater TH, Faller KME. The role of survival motor neuron protein (SMN) in protein homeostasis. Cell Mol Life Sci. 2018;75(21):3877-94. doi: 10.1007/s00018-018-2849-1
6. Ross LF, Kwon JM. Spinal Muscular Atrophy: Past, Present, and Future. Neoreviews. 2019;20(8):437-51. doi: 10.1542/neo.20-8-e437
7. Milligan JN, Blasco-Pérez L, Costa-Roger M, Codina-Solà M, Tizzano EF. Recommendations for Interpreting and Reporting Silent Carrier and Disease-Modifying Variants in SMA Testing Workflows. Genes (Basel). 2022;13:1657. doi: 10.3390/genes13091657
8. Cances C, Vlodavets D, Comi GP, Masson R, Mazurkiewicz-Bełdzińska M, Saito K, et al. Natural history of type 1 spinal muscular atrophy: A retrospec- tive, global, multicenter study. Orphanet J Rare Dis. 2022;17(1):300. doi: 10.1186/s13023-022-02455-x
9. Lusakowska A, Jedrzejowska M, Kaminska A, Janiszewska K, Grochowski P, Zimowski J, et al. Observation of the natural course of type 3 spinal muscular atrophy: Data from the polish registry of spinal muscular atrophy. Orphanet J Rare Dis. 2021;16(1):150. doi: 10.1186/s13023-021-01771-y
10. Elkins K, Wittenauer A, Hagar AF, Logan R, Sekul E, Xiang Y, et al. Georgia state spinal muscular atrophy newborn screening experience: Screening assay performance and early clinical outcomes. Am J Med Genet C Semin Med Genet. 2022;190(2):187-96. doi: 10.1002/ajmg.c.32003
11. Mercuri E, Pera MC, Scoto M, Finkel R, Muntoni F. Spinal muscular atrophy - insights and challenges in the treatment era. Nat Rev Neurol. 2020;16(12):706-15. doi: 10.1038/s41582-020-00413-4
12. Poirier A, Weetall M, Heinig K, Bucheli F, Schoenlein K, Alsenz J, et al. Risdiplam distributes and increases smn protein in both the central nervous system and peripheral organs. Pharmacol Res Perspect. 2018;6(6):e00447. doi: 10.1002/prp2.447
13. McMillan HJ, Proud CM, Farrar MA, Alexander IE, Muntoni F, Servais L. Onasemnogene abeparvovec for the treatment of spinal muscular atrophy. Expert Opin Biol Ther. 2022;22(9):1075-90. doi: 10.1080/14712598.2022.2066471
14. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: The Phase III SPR1NT trial. Nat Med. 2022;28(7):1381-9. doi: 10.1038/s41591-022-01866-4
15. Wijngaarde CA, Veldhoen ES, van Eijk RPA, Stam M, Otto LAM, Asselman FL, et al. Natural history of lung function in spinal muscular atrophy. Orphanet J Rare Dis. 2020;15(1):88. doi: 10.1186/s13023-020-01367-y
16. Schwartz O, Kölbel H, Blaschek, A, Gläser D, Burggraf S, Röschinger W, et al. Spinal Muscular Atrophy-Is Newborn Screening Too Late for Children with Two SMN2 Copies? J Neuromuscul Dis. 2022;9:389-96. doi: 10.3233/JND-220789
17. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-56. doi: 10.1016/j.nmd.2019.09.007
18. 18-Pechmann A, Behrens M, Dornbrack K, Tassoni A, Wenzel F, Stein S, et al. Improved upper limb function in non-ambulant children with sma type 2 and 3 during nusinersen treatment: A prospective 3-years smartcare registry study. Orphanet J Rare Dis. 2022;17(1):384. doi: 10.1186/s13023-022-02547-8.
19. Al-Zaidy SA, Kolb SJ, Lowes L, Alfano LN, Shell R, Church KR, et al. Avxs-101 (onasemnogene abeparvovec) for SMA1: Comparative study with a prospective natural history cohort. J Neuromuscul Dis. 2019;6(3):307-17. doi: 10.3233/JND-190403
20. Pascual-Morena C, Cavero-Redondo I, Lucerón-Lucas-Torres M, Martínez-García I, Rodríguez-Gutiérrez E, Martínez-Vizcaíno V. Onasemnogene abeparvovec in type 1 spinal muscular atrophy: A systematic review and metaanalysis. Hum Gene Ther. 2023;34(3-4):129-38. doi: 10.1089/hum.2022.161
21. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, et al. Safety and efficacy of once-daily risdiplam in type

2 and non-ambulant type 3 spinal muscular atrophy (Sunfish part 2): A phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2022;21(1):42-52. doi: 10.1016/S1474-4422(21)00367-7

22. Dangouloff T, Vrščaj E, Servais L, Osredkar D; SMA NBS World Study Group. Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go. Neuromuscul Disord. 2021;31(6):574-82. doi: 10.1016/j.nmd.2021.03.007
23. Abati E, Manini A, Comi GP, Corti S. Inhibition of myo statin and related signaling pathways for the treatment of muscle atrophy in motor neuron diseases. Cell Mol Life Sci. 2022;79(7):374. doi: 10.1007/s00018-022-04408-w
24. Cure SMA. Clinical trials 2022. Available from: https://www.curesma.org/sma-care-center-network/.
25. 25-Wirth B. Spinal muscular atrophy: In the challenge lies a solution. Trends Neurosci. 2021;44(4):306-22. doi: 10.1016/j.tins.2020.11.009
26. Johannsen J, Weiss D, Daubmann A, Schmitz L, Denecke J. Evaluation of putative CSF biomarkers in paediatric spinal muscular atrophy (SMA) patients before and during treatment with nusinersen. J Cell Mol Med. 2021;25(17):8419-31. doi: 10.1111/jcmm.16802
27. Glascock J, Darras BT, Crawford TO, Sumner CJ, Kolb SJ, DiDonato C, et al. Identifying Biomarkers of Spinal Muscular Atrophy for Further Development. Neuromuscul Dis. 2023;10(5):937-54. doi: 10.3233/JND-230054
28. Trifunov S, Natera-de Benito D, Carrera-García L, Codina A, Expósito-Escudero J, Ortez C, et al. Full-Length SMN Transcript in Extracellular Vesicles as Biomarker in Individuals with Spinal Muscular Atrophy Type 2 Treated with Nusinersen. J Neuromuscul Dis. 2023;10(4):653-65. doi: 10.3233/JND-230012
29. Magen I, Aharoni S, Yacovzada NS, Tokatly Latzer I, Alves CRR, Sagi L, et al. Muscle microRNAs in the cerebrospinal fluid predict clinical response to nusinersen therapy in type II and type III spinal muscular atrophy patients. Eur J Neurol. 2022;29(8):2420-30. doi: 10.1111/ene.15382
30. Darras BT, Crawford TO, Finkel RS, Mercuri E, De Vivo DC, Oskoui M, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. Ann Clin Transl Neurol. 2019;6(5):932-44. doi: 10.1002/acn3.779
31. Souza PVS, Pinto WBVR, Ricarte A, Badia BML, Seneor DD, Teixeira DT, et al. Clinical and radiological profile of patients with spinal muscular atrophy type 4. Eur J Neurol. 2021;28(2):609-19. doi: 10.1111/ene.14587
32. Durmus H, Yilmaz R, Gulsen-Parman Y, Oflazer-Serdaroglu P, Cuttini M, Dursun M, et al. Musclemagnetic resonance imaging in spinal muscular atrophy type 3: Selective and progressive involvement. Muscle Nerve. 2017;55(5):651-6. doi: 10.1002/mus.25385
33. Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology. 2012;79(18):1889-97. doi: 10.1212/WNL.0b013e318271f7e4
34. Pane M, Donati MA, Cutrona C, De Sanctis R, Pirinu M, Coratti G, et al. Neurological assessment of newborns with spinal muscular atrophy identified through neonatal screening. Eur J Pediatr. 2022;181(7):2821-9. doi: 10.1007/s00431-022-04470-3
35. Aragon-Gawinska K, Mouraux C, Dangouloff T, Servais L. Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening-A Systematic Review. Genes (Basel). 2023;14(7):1377. doi: 10.3390/genes14071377
36. Vill K, Schwartz O, Blaschek A, Gläser D, Nennstiel U, Wirth B, et al. Newborn screening for spinal muscular atrophy in Germany: Clinical results after 2 years. Orphanet J Rare Dis. 2021;16(1):153. doi: 10.1186/s13023-021-01783-8
37. Schorling DC, Becker J, Pechmann A, Langer T, Wirth B, Kirschner J. Discrepancy in redetermination of SMN2 copy numbers in children with SMA. Neurology. 2019;93:267-9. doi: 10.1212/WNL.0000000000007836