



Spinal Muscle Atrophy (SMA) in a 5 Years Old Girl from Macedonia: Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJPR/2023/v13i3274

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/105408>

Case Report

Received: 16/06/2023

Accepted: 22/08/2023

Published: 25/08/2023

ABSTRACT

Spinal muscular atrophies are inherited diseases in which nerve cells in the spinal cord and brainstem regress, causing progressive muscle weakness and wasting. There are five main types of spinal muscular atrophy, which are classified according to the severity of muscle weakness and wasting. Depending on the type, one may be confined to a wheelchair, and life expectancy may also be limited. Based on symptoms, the diagnosis can be proven through family history, muscle and nerve function studies, and blood tests to determine the location of the defective gene. Spinal muscular atrophies are usually inherited in an autosomal recessive manner. Thus, for a person to inherit the disease, two genes are necessary, one from each parent. The group of SMA disease in childhood can affect the brain and spinal cord as well as the peripheral nerves. We present a case of a 5 years old girl with spinal muscle atrophy and analyze the different new therapeutical options and future research in the field of spinal muscular atrophy in childhood.

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Keywords: Spinal muscular atrophy (SMA); SMA-child-treatment; SMN complexes; nerve cells.

1. INTRODUCTION

Spinal muscular atrophy (SMA) is a muscle atrophy caused by a progressive loss of motor nerve cells in the anterior horn of the spinal cord [1-18]. It occurs rarely in humans (1/10,000 born) [1-18]. The term "progressive spinal muscular atrophies" was coined by the Heidelberg neurologist Johann Hoffmann in 1893 [1-18]. The most malignant form, infantile progressive spinal muscular atrophy, was named after the Graz neurologist Guido Werdnig, who described two boys with the disease in 1891, and Johann Hoffmann. The more benign juvenile progressive spinal muscular atrophy was named after Stockholm neurologists Eric Kugelberg and Lisa Welander. They differentiated the disease from muscular dystrophies in 1956. William R. Kennedy described X-linked recessive bulbospinal muscular atrophy in 1968. Several gene defects are known to lead to inherited spinal muscular atrophy: The PIEZO2 gene contains the blueprint of a protein that acts as a mechanoreceptor to sense pressure and stretch in muscles and skin [4,7,9]. Sequence data of patients' genes revealed homozygous reading frame shifts in the PIEZO2 gene. In motor neurons, the B-Raf switch may be downregulated in SMA. Gene blueprint remodeling, or splicing, involves the SMN complex, a molecular machine consisting of at least nine different proteins. The SMN complexes are unevenly distributed in the nucleus [8,10]. They accumulate at Cajal bodies. There are no transport processes in the nucleus that bring SMN complexes to Cajal bodies. SMN complexes have unusually large numbers of phosphate groups - molecular residues with a phosphorus atom in the center. The decline of these so-called second motor neurons causes nerve signals not to be transmitted to muscles. Paralysis with the characteristics of muscle atrophy and reduced muscle tension are the result. If cranial nerves are affected, there are also limitations in swallowing, chewing and speaking functions. This is referred to as spinobulbar muscular atrophy type Kennedy (SBMA) or progressive bulbar paralysis. The following findings should be made. Decrease to extinction of the muscle reflexes. Electromyogram (EMG) with spontaneous fasciculations as resting activity and lightened patterns in the sum action potential.

Blood test: absent or altered SMN1 gene in approx. 95% of affected persons as well as

reduced number of existing SMN2 copies, Scoliosis in type I, type II and sometimes also type III.

In cases of suspected spinal muscular atrophy, genetic testing is now considered the diagnostic standard. Spinal muscular atrophies are diseases due to the demise of motor neurons (second motor neuron, alpha-motoneuron, anterior horn cell) in the spinal cord. Therefore, atrophy and weakness of the muscles occur [1-18]. In healthy individuals, muscle fibers contract due to activation by nerve fibers (innervation). As a result, depending on the number of muscle fibers involved, the muscle becomes shorter, it tenses, movement occurs. Muscle fibers that are not properly innervated by diseased nerve fibers do not contract. Just as the entire muscle becomes lankier when it is not used, when an arm is immobilized in a cast for weeks after a broken bone, individual muscle fibers become lankier when they are not activated by nerve cells. Since it is not the muscle that becomes diseased, but the nerve cells that control it, this is called muscular atrophy, in contrast to muscular dystrophy, where the muscle becomes diseased. In this case, the strength and endurance of the muscle decrease. Repairs take place in parallel. Muscle fibers not supplied by a nerve fiber can be supplied by a sprout of a preserved nerve fiber. Close to the muscle fiber, the preserved nerve fiber sprouts, forming a branch that forms a new connection (motor end plate) with the muscle fiber. Thus, the number of muscle fibers supplied innervated by a nerve fiber increases [11,13].

2. CASE PRESENTATION

The report presented a case of a 5 years old girl with spinal muscle atrophy and analyzed the different new therapeutical options and future research in the field of spinal muscular atrophy in childhood.

Molecular Genetic Analysis of a defect in the gene for spinal muscular atrophy (SMN1).

Because of suspected spinal muscular atrophy and her parents, following molecular genetic analysis was performed: Isolation of DNA by phenol-chloroform extraction/ethanol precipitation, SALSA MLPA KIT P021-B 1 and PO60-B2 with analysis of the resulting amplification products on the AV13500 genetic

analyzer. Molecular genetic analysis of the 5 years old girl revealed the presence of a deletion of exons 7 and 8 of the SMN1 gene in a heterozygous condition, which was inherited from her father. As test material isolated DNA from peripheral blood was used.

Parameter of Genetic Testing:

Method: aCGH (array Comparative Genomic Hybridization) - CytoScan 750K array.

Result: arr 10q11.22 (46,113,134-46,768,616) x3.

Interpretation: Array CGH analysis revealed a female with the presence of 3 copies of a segment of chromosome 10q (655 kb).

Additional findings were as follows: arr Hr11.22p11.21(50,867,332-55,907,685)x2 hmz;

arr7q11.23(72.760.433-76.236.949)x2 hmz;
arr15q24.1g24.3(73.912.366-77.552.562)x2 hmz

Array CGH revealed the presence of loss of heterozygosity on segments of chromosome Xr (5,040 kb); 7q (3,477 kb); 15g (3,640 kb).

The limitation of the method was present, because this method did not detect the presence of point mutations, trinucleotide repeat expansions, balanced translocations, chromosome inversions and did not determine the origin of the altered genetic material.

3. DISCUSSION

Spinal muscular atrophy is an autosomal recessive disorder [1-18]. In 95-98% of patients with SMA symptoms, the cause is a homozygous deletion of exon 7 and/or 8 of the SMN-1 gene, while in the remaining 2-5% of patients with SMA symptoms, double heterozygosity causes a deletion and a point mutation in the SMN1 gene [1-18]. Due to the rarity of the disease, an exact frequency has not been determined. It is estimated that the frequency of the disease ranges from 25,000 to 75,000 births worldwide. In Germany, it is assumed that there are approximately 1,000-1,500 patients with spinal muscular atrophy (SMA) with different types. The cause of spinal muscular atrophy is a mutation, a loss or alteration of the so-called SMN1 gene [7,11,12]. This gene forms the blueprint for the protein called "Survival of Motor Neuron"-SMN

for short. SMN is important in a wide variety of body cells and plays a crucial role, among other things, in enabling nerve cells to communicate with muscle cells and muscles to function correctly. Besides the SMN1 gene, there is a second gene in the human body to produce the SMN protein - the SMN2 gene. However, the body can only produce about 10% functional SMN protein using this gene. If the SMN1 gene fails because of the gene defect, as is the case in people with SMA, only the SMN2 gene remains to make the vital SMN protein. The amount of SMN protein that can be made depends largely on how many copies of the SMN2 gene a person with SMA has. SMA patients with a higher number of SMN2 gene copies are usually less affected by the disease. This results in the different types of the disease [1-18].

The goals of rehabilitation for neuromuscular diseases are to improve and maintain independence in mobility. Treatment is best provided by an interdisciplinary team of physicians, nurses, physical therapists, occupational therapists, speech therapists, psychologists and social workers. Outpatient therapies such as physiotherapy, occupational therapy and lopedialia are necessary to maintain existing abilities. Inpatient treatment measures lasting approximately four to six weeks are strongly recommended to improve latently existing abilities and muscular functions and to influence the course favorably. Muscle weakness causes the clinical problems of spinal muscular atrophy. In studies, 12 weeks of moderate resistance training in slowly progressive neuromuscular disease increased muscle strength by 4% to 20% without adverse effects. In the same group of patients, training with vigorous resistance for 12 weeks showed no additional benefit but overload in some patients. Evidence suggests that therapeutic methods vary in effectiveness for different neuromuscular diseases [9,11,17].

At the end of 2016, an antisense oligonucleotide (ASO) drug was approved in the USA (Spinraza, active ingredient: nusinersen; manufacturer: Biogen). EU approval followed in 2017. Developer Adrian R. Krainer of Cold Spring Harbor Laboratory received the highly endowed Breakthrough Prize in Life Sciences for it in 2019 [17]. The treatment costs \$750,000 in the first year and \$375,000 in subsequent years. Results initially available for children were confirmed in 2019 for adults up to age 65. Gene therapy treatments can correct the defect in the SMN1

gene in patients with spinal muscular atrophy by triggering alternative splicing of the related SMN2 gene, as it then forms a protein similar to the SMN1 gene product. See also gene therapy for spinal muscular atrophy. L-carnitine and valproic acid was used in a double-blinded trial [16]. In 2018, Novartis filed for approval of a novel gene therapy. An infusion of AVXS-101 was said to provide an additional 13 years of life in good health. As with the similarly acting approved tisagenlecleucel (compound name Kymriah), the price would be payable only if successful. AVXS-101 (nonproprietary name: Onasemnogene abeparvovec) was approved in the U.S. in 2019 under the compound name Zolgensma. It is priced at around \$2 million for a single dose that is expected to save lives and avoid expensive follow-up treatments. It is one of the most expensive drugs in the world per dose.

4. CONCLUSION

New therapeutic agents like nusinersen and AVXS-101 are used to treat these patients with this extremely rare disease successfully with amelioration of motor function. The drugs are very expensive, health insurance companies must confirm the treatment. In developing countries payment of these new therapies are mostly not possible. The cure of SMA children depends therefore from the goodwill of insurance companies, who support to pay the costs for this extreme expensive therapy.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mercuri E, Sumner CJ, Muntoni F, Darras BT, Finkel RS. Spinal muscular atrophy. *Nat Rev Dis Primers*. 2022 Aug 4;8(1):52.

- DOI: 10.1038/s41572-022-00380-8
PMID: 35927425.
2. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. *Orphanet J Rare Dis*. 2011 Nov 2;6:71.
DOI: 10.1186/1750-1172-6-71
PMID: 22047105; PMCID: PMC3231874.
3. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. *J Neuromuscul Dis*. 2020;7(1):1-13.
DOI: 10.3233/JND-190424
PMID: 31707373; PMCID: PMC7029319.
4. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Ender Study Group. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017 Nov 2; 377(18):1723-1732.
DOI: 10.1056/NEJMoa1702752
PMID: 29091570.
5. Acsadi G, Crawford TO, Müller-Felber W, Shieh PB, Richardson R, Natarajan N, et al. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. *Muscle Nerve*. 2021 May;63(5):668-677.
DOI: 10.1002/mus.27187
Epub 2021 Feb 16. PMID: 33501671; PMCID: PMC8248061.
6. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Cherish Study Group. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2018 Feb 15;378(7):625-635.
DOI: 10.1056/NEJMoa1710504
PMID: 29443664.
7. Masson R, Mazurkiewicz-Beldzińska M, Rose K, Servais L, Xiong H, Zanoteli E, et al. Firefish Study Group. Safety and efficacy of risdiplam in patients with type 1 spinal muscular atrophy (FIREFISH part 2): secondary analyses from an open-label trial. *Lancet Neurol*. 2022 Dec;21(12):1110-1119.
DOI: 10.1016/S1474-4422(22)00339-8
Epub 2022 Oct 14. PMID: 36244364.
8. Mercuri E, Baranello G, Boespflug-Tanguy O, De Waele L, Goemans N, Kirschner J, et al. Sunfish Working Group. Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. *Eur J Neurol*. 2023 Jul;30(7): 1945-1956.

- DOI: 10.1111/ene.15499
Epub 2022 Aug 1. PMID: 35837793.
9. Rudnicki SA, Andrews JA, Duong T, Cockroft BM, Malik FI, Meng L, et al. Reldesemtiv in Patients with Spinal Muscular Atrophy: A Phase 2 Hypothesis-Generating Study. *Neurotherapeutics*. 2021 Apr;18(2):1127-1136. Doi: 10.1007/s13311-020-01004-3. Epub 2021 Feb 23. Erratum in: *Neurotherapeutics*. 2021 Jul;18(3):2130. PMID: 33624184; PMCID: PMC8423982.
 10. Bonanno S, Giossi R, Zanin R, Porcelli V, Iannacone C, Baranello G, et al. Amifampridine safety and efficacy in spinal muscular atrophy ambulatory patients: A randomized, placebo-controlled, crossover phase 2 trial. *J Neurol*. 2022 Nov;269(11):5858-5867. DOI: 10.1007/s00415-022-11231-7 Epub 2022 Jun 28. PMID: 35763114; PMCID: PMC9243784.
 11. Oskoui M, Day JW, Deconinck N, Mazzone ES, Nascimento A, Saito K, et al. Sunfish Working Group. Two-year efficacy and safety of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA). *J Neurol*. 2023 May;270(5):2531-2546. DOI: 10.1007/s00415-023-11560-1 Epub 2023 Feb 3. Erratum in: *J Neurol*; 2023 Apr 18. PMID: 36735057; PMCID: PMC9897618.
 12. Acsadi G, Crawford TO, Müller-Felber W, Shieh PB, Richardson R, Natarajan N, et al. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. *Muscle Nerve*. 2021 May;63(5):668-677. DOI: 10.1002/mus.27187 Epub 2021 Feb 16. PMID: 33501671; PMCID: PMC8248061.
 13. 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 Apr 17;6(5):932-944. DOI: 10.1002/acn3.779 PMID: 31139691; PMCID: PMC6530526.
 14. Mercuri E, Baranello G, Boespflug-Tanguy O, De Waele L, Goemans N, Kirschner J, et al. Sunfish Working Group. Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. *Eur J Neurol*. 2023 Jul;30(7):1945-1956. DOI: 10.1111/ene.15499 Epub 2022 Aug 1. PMID: 35837793.
 15. Kissel JT, Elsheikh B, King WM, Freimer M, Scott CB, Kolb SJ, et al. Project Cure Spinal Muscular Atrophy Investigators Network. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. *Muscle Nerve*. 2014 Feb;49(2):187-92. DOI: 10.1002/mus.23904 PMID: 23681940; PMCID: PMC3888833.
 16. Swoboda KJ, Scott CB, Crawford TO, Simard LR, Reyna SP, Krosschell KJ, et al. Project Cure Spinal Muscular Atrophy Investigators Network. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One*. 2010 Aug 19;5(8):e12140. DOI: 10.1371/journal.pone.0012140 PMID: 20808854; PMCID: PMC2924376.
 17. Ohmura T, Saeki S, Ogiwara K, Tobita K, Ling Y, Torii S. [Pharmacological and clinical profile of spinal muscular atrophy (SMA) therapeutic drug nusinersen (Spinraza®)]. *Nihon Yakurigaku Zasshi. Japanese*. 2018;152(3):147-159. DOI: 10.1254/fpj.152.147 PMID: 30185733.
 18. Weaver MS, Hanna R, Hetzel S, Patterson K, Yuroff A, Sund S, Schultz M, Schroth M, Halanski MA. A Prospective, Crossover Survey Study of Child- and Proxy-Reported Quality of Life According to Spinal Muscular Atrophy Type and Medical Interventions. *J Child Neurol*. 2020 Apr;35(5):322-330. DOI: 10.1177/0883073819900463 Epub 2020 Feb 3. PMID: 32009500.

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Peer-review history:

The peer review history for this paper can be accessed here:
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