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Diagnosis SMA Disease and Making Drugs Available

Selin KÖSEOĞLU - FMV Private Ispartakule Işık High School

ABSTRACT

SMA (Spinal Muscular Atrophy) which is an autosomal recessive neuromuscular disease (Cherry, J. J., Evans, M. C., Ni, J., Cuny, G. D., Glicksman, M. A., & Androphy, E. J. ,2012). It is the result of the homozygote gene loss in the SMN1 (survival motor neuron gen 1) gene. Symptoms and medication used may vary depending on their type. The SMA has 4 types, which are: SMA type 1 can be diagnosed either during the last period of pregnancy or in baby's of 6 months or younger according to babies movement declaration. In type 2 , symptoms can occur within 6-18 months. When the baby's progress is in the course of normal process after a while cannot walk unsupportedly and needs support to walk. When it comes to type 3 symptoms can occur from 18 month till adolescence. In type 4 can be seen in adults. It can be seen rarely than the other types. In this article, the ability of diagnosis to translate genetic diagnosis into standard procedure before individuals get married also has been an idea of the ability to make their treatment more suitable and accessible. Previous researches and articles written about the content of the drug were examine through a literature review. While the 3 methods considered in terms of changing the content and the type of drug are; simplification the content of the drug, whether gene therapy can be given to patience from donors who has dominant homozygote or not, the more appropriate manufacture of the drug by reducing commercial profit. It has been concluded that: The SMN1 gene has an important location in the person, so it cannot be removed from donors. It has been established that pharmaceutical content is developed differently, depending on SMA types, and that any commercial profit should be reduced, even if it is simplified.

Keywords: *Drug with Commercial Profit, Early Diagnosis, SMA, SMN1 Gene, Standard Procedure, Treatment, Types of SMA*

1. Introduction

It was found in the 1890s by two scientists, Johann Hoffman and Guido Werdnig. In 1995, the gene that caused the disease was found by Dr. Judith Melki and Survival Motor Neuron (SMN), the vital gene. SMA is an autosomal recessive neuromuscular disease that we hear about the most today. One in 50 people today is a carrier of SMA disease however, although this does not have a bad effect on the person, it is likely to be found in children or grandchildren. Although symptoms vary according to the types of SMA, their general symptoms are muscle weakness, decreased development, etc. SMA types are divided into types according to their starting age. Type 1 occurs in babies 0-6 months old, while type 4 shows symptoms in adulthood (Prior , 2019).

SMN1

The SMN1 gene is responsible for the production of survival motor neuron (SMN) protein, which regulates the health and normal function of motor neurons. If the SMN protein cannot be produced, motor neurons will lose out and signals will not be transmitted to the brain. SMA disease is also caused by a mutation of the SMN1 gene.However, it is not yet known why motor neurons are so susceptible to the reduction of the SMA protein. In some studies, it has been shown that the deficiency of the SMN protein causes impairment in the function and structure of the axons and dendrites, resulting in loss of neurons. However, the SMN2 gene is also present.This gene is also known as the backup mechanism of the SMN1 .Although similar to SMN1, only a small fraction of the SMN protein (up to 10%) is functional (Corcia, 2006). Therefore, the functional part produced by the SMN2 gene does not have enough effect for the motor neurons in the central nervous system to continue their health and function. .Other factors that may cause SMA are not yet known.

SMA disease diagnosis

In the diagnosis of the disease; If there is someone with a carrier or SMA in the family, an amniocentesis test is performed to see if the baby is SMA or not. Amynosynthesis test is used to determine whether a person has a chromosomal disease. In SMA patients, it's 5. this disease is detected by the damage of the chromosome. If damage to the person's 5th chromosome is detected, it is understood that the SMN 1 protein cannot be produced directly. In the conduct of this test, some fluid is taken from the fluid that the fetus swims in before birth with surgical intervention. Genetic examinations are carried out (Eddleman, 2006). In type 3 and type 4, in case of doubt, the SMN1 gene in the tissue taken from the suspicious patient is examined (Laessig, Schwartz, Paskey, 1972).

Treatment of SMA

In the treatment of SMA, molecular biologists use gene therapy through the viral vector of the gene consisting of artificial nucleotides (Coffin, Hughes, Varmus, 1997). There are 6 most commonly known drugs for this treatment. Although the content of these drugs is similar, the drugs applied to the types may differ (Russmann, 2003). According to the FDA, there is currently no drug that differs in content.

2. SMA types and it’s drugs

There are 4 types of SMA. And it's treated based on the damage to the person's SMN1 gene (SMA Foundation, 2019). Zolgensma, even if it passes as a drug, actually represents a complete whole course of treatment. The amount to be paid for the drug Zolgensma for the treatment of a single patient is $2.1 million. Spinraza offers a lifelong treatment that is taken four times a year.

The amount to be paid in 10 years for the drug, which is 750 thousand in the first year and then 350 thousand dollars annually, is approximately 4 million dollars.

At this point, the purpose of this article is stated: it is very important to reduce the commercial profit. Many companies also deny this. Novartis says that it offers an SMA treatment that will result in one shot, and the company deserves this financial gain in return for the spiritual gain that the drug gives to the family and patient relatives. According to the FDA, there is currently no new drug with new content or under examination.

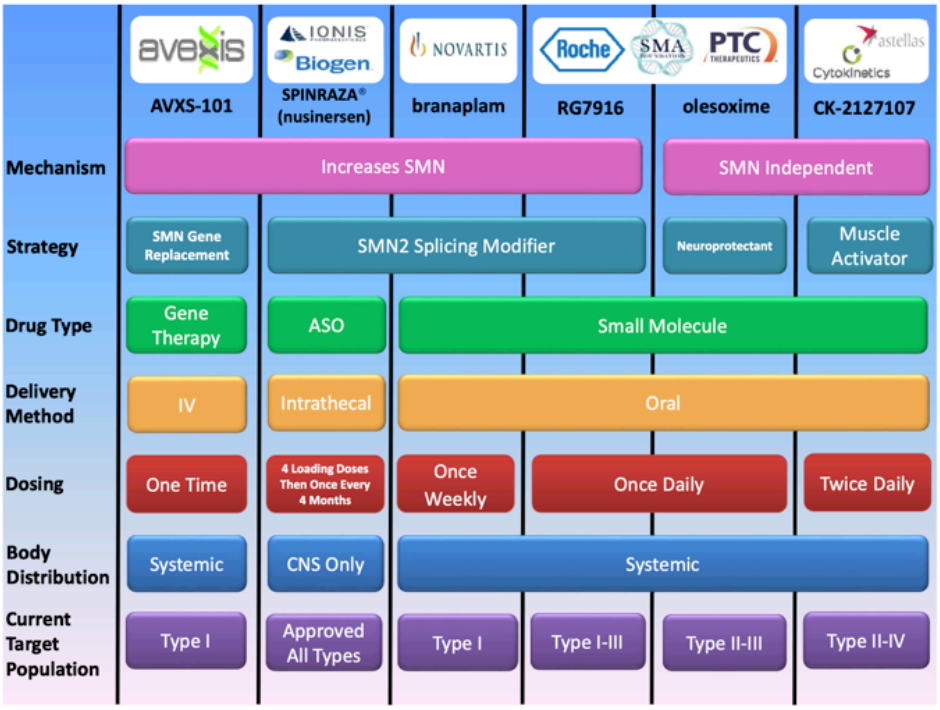
Table 1. All 4 types of SMA we see in the table differ in both the time of appearance and the estimated life expectancy. For example, in type 1, the baby cannot sit, while the type 2 patient may sit down but has trouble walking.

Type	Age of Onset	Maximal Motor Milestone	Motor Ability and Additional Features	Prognosis[c]
SMA 0	Before birth	None	Severe hypotonia; unable to sit or roll[a]	Respiratory insufficiency at birth; death within weeks
SMA I	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit or roll[b]	Death/ventilation by 2 years
SMA II	6 to 18 months	Sitting	Proximal weakness; unable to walk independently	Survival into adulthood
SMA III	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
SMA IV	>30 years or 10 to 30 years	Normal	Mild motor Impairment	Normal life span

[a]Need for respiratory support at birth; contractures at birth, reduced fetal movements.
[b]Ia joint contractures present at birth; Ic may achieve head control.
[c]Prognosis varies with phenotype and supportive care interventions.

Source: J Curr Pediatr 2016;14:18-22

Table 2. The drugs used in SMA also differ according to the types.For example, AVSX-101 results in a single dose in type 1 patients, while Olesoxime is for both type 2 and type 3 and the dosages differ.



Source: SMA Foundation (2019).

4. Discussion and Result

According to Turkish Health Minister Fahrettin Koca, 6000 SMA patients are born in Turkey every year.. In order to prevent this and to take the necessary precautions, the priority solution is to procedure the genetic diagnosis on individuals before marriage.If the family tree is established, if it is determined whether the children to be born will be SMA or not, the family will be prepared for this and the problems that may be encountered in the future are considered and measures can be taken.After considering the fact that the drugs can be made more affordable to patients, it has been understood that the content of the drug is generally similar in all. When it is understood that such drugs are made to make commercial profits, states need to reach an agreement on this issue, and reducing the financial burden that patients' relatives will be under for a lifetime, regardless of their socioeconomic level, may be a solution for this great problem experienced in the world. At the same time, it is possible to start local drug production in Turkey. If the state can provide molecular biologists trained in Turkey with the opportunity to receive education in places where the field of the pharmaceutical industry is good, many willing people will come out. In the meantime, if the local pharmaceutical industry and universities reach an agreement, Turkey may have its own local medicine. After all, if the drug is produced in Turkey, it may be a happy news for everyone that it contributes to both Turkey and the patients in Turkey. If the state, faculties and local pharmaceutical industries provide this opportunity, we will not have to watch the spiritual collapse of patients' relatives.

References

Aga Lewelt, K. J. (2010). Compound muscle action potential and motor function in children with spinal muscular atrophy. *Muscle & Nerve*. doi:10.1002/mus.21838

Amelie K Gubitz, W. F. (2004). The SMN complex, Experimental Cell Research. (296), 51-56. Taken from this address https://doi.org/10.1016/j.yexcr.2004.03.022.

Authors Kathryn J. Swoboda, T. W. (2005). Title Natural history of denervation in SMA: Relation to age,SMN2 copy number, and function. *Published in Annals of Neurology*. doi:10.1002/ana.20473

Bach, J. R. (2008). The use of mechanical ventilation is appropriate in children with genetically proven spinal muscular atrophy type 1: the motion for,. 45-50. Taken from this address https://doi.org/10.1016/j.prrv.2007.11.003

Basil T. Darras, H. R. (2014). Imprint: Academic Press. Received on November.

Bach, J. R. (2010). Spinal muscular atrophy type 1: Management and outcomes. *Pediatric Pulmonology*(34), 16-22. Taken from this address https://doi.org/10.1002/ppul.10110

Brichta, L. H. (2006). In vivo activation of SMN in spinal muscular atrophy carriers and patients treated with valproate. *Annals of neurology*, 970-975. Taken from this address https://doi.org/10.1002/ana.20836

Brzustowicz, L. L. (1990). Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome. *Nature*, 540–541. Taken from this address https:// doi.org/10.1038/344540a0

Coffin, J. M., Hughes, S. H., & Varmus, H. E. (Eds.). (1997). *Retroviruses*. Cold Spring Harbor Laboratory Press.

Corcia, P. C. (2009, November 16). The importance of the SMN genes in the genetics of sporadic ALS. *Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases*, 436-440. doi:10.3109/17482960902759162

Courtens W, J. A. (2002). Infantile spinal muscular atrophy variant with congenital fractures in a female neonate: evidence for autosomal recessive inheritance. *Journal of Medical Genetics*, 74-77.

Eddleman, K. A., Malone, F. D., Sullivan, L. P., Dukes, K. P., Berkowitz, R. L., Kharbutli, Y. M., . . . Dugoff, L. M. (2006, November). *Pregnancy Loss Rates After Midtrimester Amniocentesis*, Obstetrics & Gynecology. (108). doi:doi: 10.1097/01.AOG.0000240135.13594.07

Farrar, M. K. (2015). The Genetics of Spinal Muscular Atrophy: Progress and Challenges. *Neurotherapeutics* (12), 290–302. Taken from this address https://doi.org/10.1007/s13311-014-0314-x

Frédérique Souchon, L. R. (1996). Clinical and genetic study of chronic (types II and III) childhood onset spinal muscular atrophy. *Neuromuscular Disorders*, 419-424. Taken from this address https://doi.org/10.1016/S0960-8966(96)00379-3

H.M. Blauw, C. B. (2012). SMN1 gene duplications are associated with sporadic ALS. *Neurology*, 776-780. doi:10.1212/WNL.0b013e318249f697

Heidi R. Fuller, T. H. (2016). Commonality amid diversity: Multi-study proteomic identification of conserved disease mechanisms in spinal muscular atrophy,. *Neuromuscular Disorders*, 560-569. Taken from this address https://doi.org/10.1016/j.nmd.2016.06.004

Iannaccone, S. T. (2000). Prospective Analysis of Strength in Spinal Muscular Atrophy. *Journal of Child Neurology*, 97–101. Taken from this address https:// doi.org/10.1177/088307380001500207

Jim S. Wu, B. T. (2010). Assessing spinal muscular atrophy with quantitative. *Neurology*, 526-531. doi:10.1212/ WNL.0b013e3181eccf8f

Johnson, W. G.-W.-K.-R. (1982). Juvenile spinal muscular atrophy: A new hexosaminidase deficiency phenotype. *Annals of Neurology JA*, 0364-5134. Taken from this address https://doi.org/10.1002/ana.410110103

Karni, A. A.-N. (No date). Hexosaminidase a deficiency manifesting as spinal muscular atrophy of late onset. *Annals of Neurology JA*, 453. Taken from this address https://doi.org/10.1002/ana.410240316

Kaufmann, P. M. (2007). International Coordinating Committee for SMA Subcommittee on SMA Clinical Trial Design. *The International Coordinating Committee*, 499–505. Taken from this address https://doi.org/10.1016/j.nmd.2006.12.001

Klaus Zerres, S. R.-S.-P. (1997). A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. *Journal of the Neurological Sciences*, 67-72. Taken from this address https://doi.org/10.1016/S0022-510X(96)00284-5

Kniffin, C. L. (2021, March 27). Online Mendelian Inheritance in Man. *Spinal Muscular Atrophy*. On August 21, 2007 Taken from this address http://www.ncbi.nlm.nih.gov/omim/

L. Brichta, Y. H. (2003). Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy. *Human Molecular Genetics*(82), 2481–2489. Taken from this address https://doi.org/10.1093/hmg/ ddg256

Luca Cartegni, M. L. (2006). Determinants of Exon 7 Splicing in the Spinal Muscular Atrophy Genes, SMN1 and SMN2. *The American Journal of Human Genetics*, 63-77.

Matthew C. Evans, J. N. (2012, January 10). Find in PubMed. *Journal of Biomolecular Screening*(17).

Merlini, L.A. - G. - B. - C. - S. (1989). Scoliosis in spinal muscular atrophy: Natural history and management. *Developmental Medicine & Child Neurology*, 508. Taken from this address https://doi.org/10.1111/j.1469-8749.1989

Michael Puruckherr, J. B. (2004). Severe Obstructive Sleep Apnea in a Patient With Spinal Muscle Atrophy. *Chest*, 1705-1707. Taken from this address https://doi.org/10.1378/chest.126.5.1705

Miles JM, G.-B. E. (1993, Jul). Pathological case of the month. Type 3 spinal muscular atrophy (Kugelberg-Welander disease). *American Journal of Diseases of Children (1960)*, 793-794.

N.H. Thomas, V. D. (1994). The natural history of type I (severe) spinal muscular atrophy. *Neuromuscular Disorders*, 497-502. Taken from this address https://doi.org/10.1016/0960-8966(94)90090-6

P. Corcia, W. C.-M. (2006). SMN1 gene, but not SMN2, is a risk factor for sporadic ALS. *Neurology*, 1147-1150.

Paul Renbaum, E. K.-L. (2009). The American Journal of Human Genetics. (85), 281-289. Taken from this address https://doi.org/10.1016/j.ajhg.2009.07.006

Prior TW, L. M. (2019, November 14). *Finanger E. Spinal Muscular Atrophy*.

Prior TW, R. B. (1993-2012). *GeneReviews at GeneTests*. On April 26, 2021 NCBI: Taken from this address www.genetests.org.

R.G. Miller, D. M. (2001). A placebo-controlled trial of gabapentin in spinal muscular atrophy. *Journal of the Neurological Sciences* (191), 127-131. Taken from this address https://doi.org/10.1016/S0022-510X(01)00632-3

Ronald H Laessig, T. H. (1972). Determination of SMA-Mark X1,2 Set Points for Bilirubin by Standard Addition Technique. *Clinical Chemistry*(18), 48-51. Taken from this address https://doi.org/10.1093/clinchem/18.1.48

Serra - Juhe, C. T. (2019, March 07). Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors. *Eur J Hum Genet*. doi: https://doi.org/10.1038/s41431-019-0415-4

Seward B. Rutkove, J. M. (2010, November). Characterizing spinal muscular atrophy with electrical impedance myography. *Muscle & Nerve*. doi:10.1002/mus.21784

Stephen J. Kolb, M. P. (2015). Spinal Muscular Atrophy. 831-846. Taken from this address https://doi.org/10.1016/j.ncl.2015.07.004

Sugarman, E. N. (2012). Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72400 specimens. *Eur J Hum Genet*, 27-32. Taken from this address https://doi.org/10.1038/ejhg.2011.134

Suzie Lefebvre, L. B. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*, 155-165. Taken from this address https://doi.org/10.1016/0092-8674(95)90460-3

Talbot, K. (1999). Spinal muscular atrophy. *JIMD*, 311-316.

Tiller, G. E. (2007, August 21). Online Mendelian Inheritance in Man. *Spinal Muscular Atrophy*. On March 27, 2021 Taken from this address http://www.ncbi.nlm.nih.gov/omim/

Urbánek K, C. J. (1990). ACTH and steroids in Kugelberg-Welander disease. *Acta Univ Palacki Olomuc Fac Med.*, 147-150.

Uwe Mellies, C. D.-S. (2004). Sleep disordered breathing in spinal muscular atrophy. *Neuromuscular Disorders*, 797-803. Taken from this address https://doi.org/10.1016/j.nmd.2004.09.004

VA, M. (2011, November 15). Online Mendelian Inheritance in Man . *Spinal Muscular Atrophy*. On April 24, 2021 Taken from this address http:// www.ncbi.nlm.nih.gov/omim/

Vernon, H. J. (2011, December 05). Online Mendelian Inheritance in Man. *Spinal Muscular Atrophy*.On April 22, 2021 Taken from this address http:// www.ncbi.nlm.nih.gov/omim/

Yang, W. H. (2019). Prediction of key gene function in spinal muscular atrophy using guilt by association method based on network and gene ontology. *Experimental and Therapeutic Medicine*, 2561-2566. Taken from this address https://doi.org/10.3892/ etm.2019.7216

Yen-Bin Liu, W.-J. C.-T. (1999). Atrial standstill in a case of Kugelberg-Welander syndrome with cardiac involvement: an electrophysiologic study. *International Journal of Cardiology*, 207-210. Taken from this address https://doi.org/10.1016/S0167-5273(99)00078-9