http://mnj.ub.ac.id/
DOI: 10.21776/ub.mnj.2021.007.02.11
eISSN: 2442-5001 **pISSN:** 2407-6724
Accredited by DIKTI Decree No: 21/E/KPT/2018

MALANG NEUROLOGY JOURNAL MNJ

CASE REPORT OPEN ACCESS

A CASE OF NEONATAL SPINAL MUSCULAR ATROPHY WITH SEPSIS LIKE PRESENTATION

Oznur Yilmaz Gondal[1], Ebru Yalin Imamoglu[2], Elif Yuksel Karatoprak[3]

Correspondence: *oznuryilmaz@yahoo.com*
[1]*Beykent University, Faculty of Medicine, Department of Pediatrics, Istanbul, Turkey*
[2]*Istanbul Medeniyet University, Faculty of Medicine, Clinic of Neonatalogy, Istanbul, Turkey*
[3]*Istanbul Medeniyet University, Faculty of Medicine, Clinic of Pediatric Neurology, Istanbul, Turkey*

Article History:
Received: September 26, 2020
Accepted: April 21, 2021
Published: July 1, 2021

Cite this as:
Gondal OY, Imamoglu EY, Karatoprak EY. A case of neonatal spinal musular atrophy with sepsis like presentation. Malang Neurology Journal; 2021.7: 137-139. http://dx.doi.org/10.21776/ub.mnj .2021.007.02.11

ABSTRACT

Introduction: Spinal Muscular Atrophy (SMA) is a progressive neuromuscular disease causing degeneration of nerves at anterior horn of spinal cord. The most common and severe form is SMA type 1 which starts before 6 months of age. Patients do not survive more than 2 years and usually die of respiratory failure. Although there was no specific cure for the disease until the last 3 years, new treatment modalities, with the improving gene-technology have given good results in progression of the disease and early diagnosis and treatment gained importance.
Case: A male 28-days-old baby visited our clinic for routine physical examination and was found to be slightly hypotonic. He had decreased strength in sucking and crying and had slowing in motion in the last 4-5 days. C-reactive protein level was slightly elevated. Since he had a sepsis-like presentation, he was referred to neonatal intensive care unit (ICU). He was given antibiotics and monitored. However, in follow-up he became more hypotonic and deep tendon reflexes were lost. He was diagnosed as SMA type I and was referred for nusinersen (antisense-oligonucleotide) treatment. After treatment, he showed a good progress in motor functions and still does not need any respiratory support.
Conclusions: We presented this case to draw attention to SMA in differential diagnosis of hypotonic newborns with sepsis-like presentation and emphasize the importance of early diagnosis and treatment.

Keywords: Spinal Muscular Atrophy, neonatal sepsis, treatment, nusinersen

Introduction

Spinal Muscular Atrophy (SMA) is an inherited neuromuscular disease caused by deletions in Survival Motor Neuron (SMN) gene on chromosome 5q13.1 SMN gene encodes SMN protein, which is essential in survival of motor neuron. The incidence according to statistics in USA is 1/5000-1/11000, and the carrier frequency is 1/54.2,3 The incidence is 1/3900-1/16.000 in European countries.4 It has four main phenotypes.5 The most common and severe type-SMA type-I (Werdnig Hoffman Disease), starts before 6 months. Patients if untreated, have life expectancy of less than 2 years and usually die of respiratory failure. An antisense oligonucleotide, named nusinersen opened e new era in treatment for the last three years and increased the life-expectancy and motor abilities in patients.

Case Report

A male baby born at 37th week of gestation by C/S, from a Spanish-origin mother and Turkish father, with birth weight of 2960 g, was first examined in pediatrics clinic at postnatal day 4. Mother had history of one abortion. The newborn was orally fed and the physical examination was normal except minimal icterus. In follow-up, bilirubin levels were10.8 mg/dl, 13.4 mg/dl and 9.8mg/dl at 4th, 8th and 12th days, respectively. Weight gain was good and physical examination findings were normal. At 19th day, the baby admitted to hospital with the complaint of blocked nose. The mother also had symptoms of common cold. The physical examination of the baby was normal except nasal congestion and nasal serum physiologic was advised. At 28th day, the family brought the baby to hospital for circumcision and visited Pediatrics clinic for routine control before the procedure. They had no complaint; the symptoms of common cold were relieved. In physical examination, the weight gain was good, icterus had diminished but the baby was slightly hypotonic and there was distension in abdomen. When questioned in detail, mother told about decreased strength in sucking and crying and slowing in motion in the last 4-5 days. Blood glucose level was checked and was found to be normal. Since the baby had hypotonia and decreased sucking, he was suspected of sepsis at first step and blood samples were taken. Urea, kreatinin, AST, ALT levels and blood electrolytes were normal, however C-reactive protein (CRP) level was slightly high and the newborn was referred to neonatal intensive care unit (ICU) of a university hospital for further analysis and treatment. In neonatal ICU, ampicillin and gentamycin treatment was started intravenously due to weak suck, mild hypotonia and slightly high CRP level. Cranial and abdomina

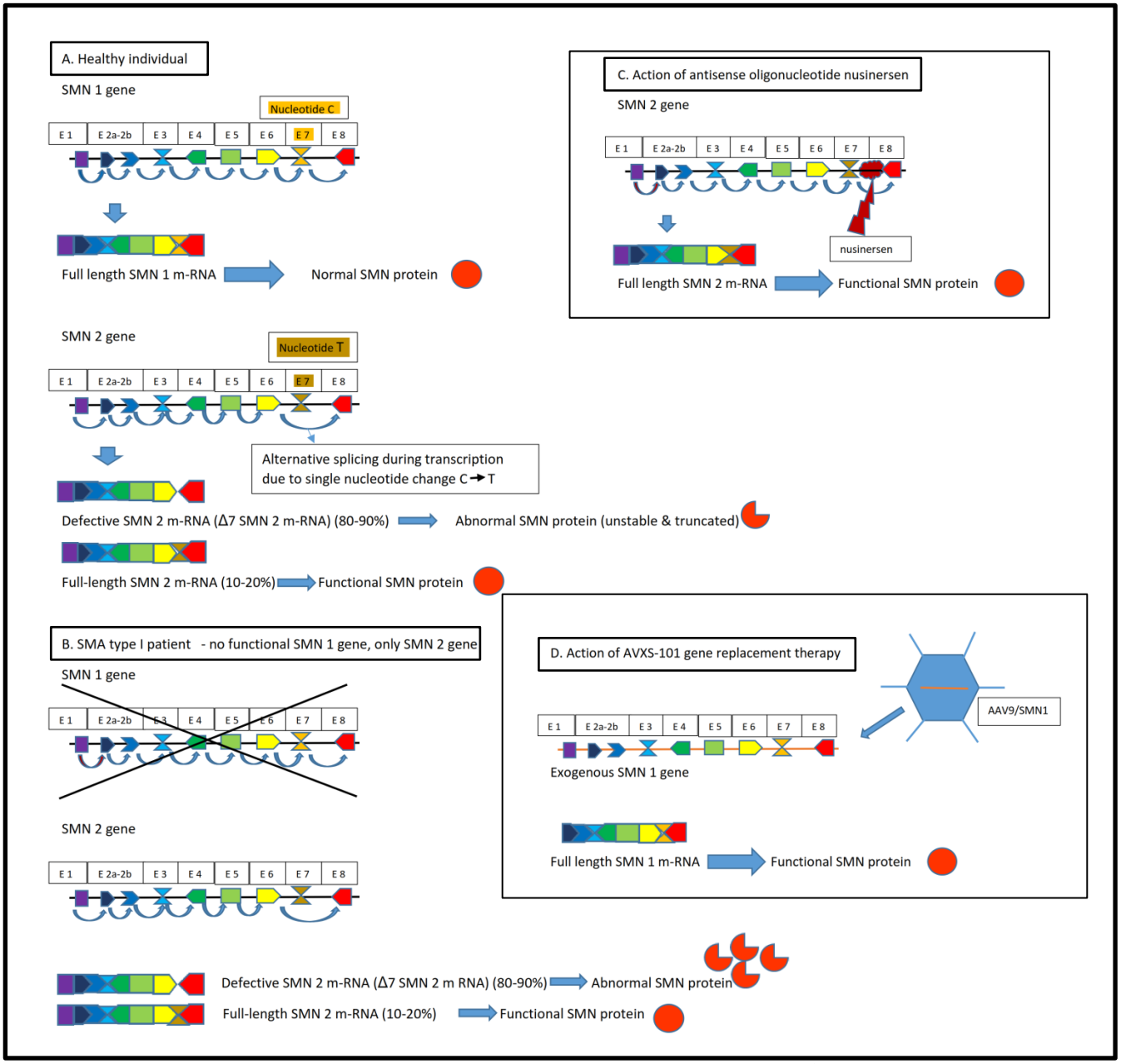

Figure 1. Genetics and treatment modalities in Spinal Muscular Atrophy (SMA). A. In a healthy individual, there are two types of Survival Motor Neuron (SMN) genes that code SMN protein: SMN1 gene and SMN2 gene. Full length SMN1 m-RNA is produced by SMN1 gene that results in production of healthy SMN protein. SMN2 gene differs from SMN1 gene by a single nucleotide in exon 7 (C-to-T). This causes alternative splicing during transcription (at a chance of 80-90%), resulting in formation of a defective m-RNA that lacks exon 7 (Δ7 SMN2 m-RNA). This defective m-RNA produces abnormal and non-functional SMN protein. B. In SMA type-1 patients, there is no SMN1 gene, therefore, very small amount of functional SMN protein is produced by SMN2 gene. C. Antisense oligonucleotide nusinersen binds to malfunctioning region of SMN2 gene, just after exon 7 and prevents alternative splicing during transcription resulting in formation of full-length m-RNA and functional SMN protein. D. In AVXS-101 gene therapy, healthy SMN gene is introduced into human body, encapsulated by an Adeno-associated vector virus (scAAV9). The virus introduces the gene into target cells in human body, resulting in restoration of genetic functions, but doesn't itself integrate in human genome.

ultrasonography were normal. There was a wide patent foramen ovale and left to right shunt in echocardiography. C-reactive protein level was found decreased to normal in two days. Urine and blood culture was sterile. Biochemical parameters, thyroid function tests, blood ammonium levels, viral screening for TORCH-S, blood amino acid profile and TANDEM-MS were normal. Ampicillin-gentamycin treatment was continued for 10 days and stopped. During the treatment, the baby became more hypotonic and deep tendon reflexes were lost. A neuromuscular disease was suspected and he was consulted to a pediatric neurologist. Peripheral blood sample was taken for SMA and analyzed by Multiplex-Ligation Dependent Probe Amplification (MLPA) technique. Homozygous deletion was detected in exon 7 and exon 8 in SMN1 gene at postnatal day 45 and he was diagnosed as SMA type I. He had two copies of SMN2 gene. When questioned after diagnosis, mother told about her aunt with an undiagnosed muscle disease. The baby was referred to the university hospital for intrathecal nusinersen (antisense-oligonucleotide) treatment and first dose was given at postnatal 60th day. At the last visit, he was 15 months-old, completed the 6th dose of nusinersen treatment, didn't need respiratory support, could sit with support, used hands and had improvement in motor functions.

Discussion

SMA type I is an autosomal recessively inherited, progressive neuromuscular disease causing degeneration of

nerves at anterior horn of spinal cord (alpha motor neurons) and leading to weakness and paralysis of the innervated muscles. It is the most common and severe type of spinal muscular atrophy, with the earliest onset. It starts before 6 months and the first symptoms are hypotonia and respiratory distress. The patients do not achieve head control and cannot sit. In physical examination, spontaneous movement against gravity is decreased and deep tendon reflexes are lost. The patients usually cannot survive beyond 2 years of age and die due to respiratory failure. Most severe forms start with decreased movement in intrauterine period and severe joint contractures and hypotonia can be seen at birth.[6] Our case was asymptomatic at birth. Mild hypotonia was recognized at 4th week in routine physical examination and the family members were not aware of it until they were questioned in detail. Since he had a slightly increased CRP level, he was suspected of sepsis and referred to ICU for treatment. During treatment for sepsis, there was no improvement, even worsening of hypotonia and he was suspected of a neuromuscular disease. Treatment with nusinersen was started in 2 weeks after the diagnosis was confirmed.

Treatment of SMA was only symptomatic until recently. Nusinersen treatment opened a new era in the management of SMA. Early diagnosis and early initiation of treatment before spinal motor neuron degeneration gained importance in the prognosis of the disease.[7-10] In patients with SMA type I, SMN1 gene is mutated or absent and SMN 2 gene produces only a little amount of functioning SMN protein. This is because of alternative splicing of SMN2 gene during transcription due to a single nucleotide change in exon 7. Nusinersen binds to malfunctioning region of SMN 2 gene, leads to production of healthy SMN proteins and prevents the motor neuron death (Figure 1). Therefore, the number of SMN2 genes are important for the efficacy of the treatment. The treatment is used for the last 3 years and provides improvement of motor functions in patients with SMA type 1.[7-10] Our patient was also diagnosed and received treatment at a relatively early age (at 2 months) and showed improvement in motor functions and did not need any respiratory support. It has become increasingly important to keep these babies alive, as new treatment strategies like gene therapy (AXVS-101) are also in progress which aims delivery of a functional human SMN gene into target human motor neuron cells through a viral capsid (Figure 1).[11,12]

Conclusion

In conclusion, this case was reported to draw attention to SMA, in the differential diagnosis of hypotonic babies with sepsis-like presentation and to emphasize the importance of early diagnosis for the efficacy of the nusinersen treatment.

Acknowledgment

None

Conflict of Interest

No conflict of interest is declared by the authors.

References

1. Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell; 1995. 80:155–65. DOI: 10.1016/0092-8674(95)90460-3
2. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin; 2015. 33(4):831-46. DOI: 10.1016/j.ncl.2015.07.004. PMID: 26515624; PMCID: PMC4628728.
3. Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet; 2012. J20(1):27-32. DOI: 10.1038/ejhg.2011.134. Epub 2011 Aug 3. PMID: 21811307; PMCID: PMC3234503.
4. VerhaartIngrid EC, Robertson A, Leary R, McMacken G, Konig K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol; 2017. 264: 1465–73. DOI 10.1007/s00415-017-8549-1.
5. Munstat TL, Davies KE. International SMA consortium meeting. Neuromuscul Disord; 1992. 2: 423–8. DOI: 10.1016/S0960-8966(06)80015-5
6. Grotto S, Cuisset JM, Marret S, Drunat S, Faure P, Audebert-Bellanger S, et al. Type 0 Spinal Muscular Atrophy: Further Delineation of Prenatal and Postnatal Features in 16 Patients. J Neuromuscul Dis; 2016. 29: 3(4):487-95. DOI: 10.3233/JND-160177. PMID: 27911332.
7. Paton DM. Nusinersen: antisense oligonucleotide to increase SMN protein production in spinal muscular atrophy. Drugs Today (Barc); 2017. 53(6): 327-37. DOI: 10.1358/dot.2017.53.6.2652413.
8. Pechmann A, Langer T, Schorling D, Stein S, Vogt S, Schara U, et al. Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany. Neuromuscul Dis; 2018. 5(2): 135-43. DOI: 10.3233/JND-180315.
9. Dabbous O, Maru B, Jansen JP, Lorenzi M, Cloutier M, Guérin A, et al. Survival, Motor Function, and Motor Milestones: Comparison of AVXS-101 Relative to Nusinersen for the Treatment of Infants with Spinal Muscular Atrophy Type 1. Adv Ther; 2019. 36 (5): 1164-76. DOI: 10.1007/s12325-019-00923-8. Epub 2019 Mar 16.
10. Albrechtsen SS, Born AP, Boesen MS. Nusinersen treatment of spinal muscular atrophy - a systematic review. Dan Med J; 2020. 67(9):A02200100. PMID: 32800069.
11. Al-Zaidy SA, Mendell JR. From Clinical Trials to Clinical Practice: Practical Considerations for Gene Replacement Therapy in SMA Type 1. Pediatr Neurol; 2019.100:3-11. DOI: 10.1016/j.pediatrneurol.2019.06.007
12. Stevens D, Claborn MK, Gildon BL, Kessler TL, Walker C. Onasemnogene Abeparvovec-xioi: Gene Therapy for Spinal Muscular Atrophy. Ann Pharmacother; 2020. 54(10):1001-9. DOI: 10.1177/1060028020914274. Epub 2020 Mar 23. PMID: 32204605.