International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Ali PBG. Int J Reprod Contracept Obstet Gynecol. 2025 Nov;14(11):4004-4008
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20253552

Case Report

Homozygous SMN1 gene deletion as a cause of intrauterine and neonatal mortality

Parisa Batul Ghulam Ali*

Department of Pharmacy, Benazir Bhutto Shaheed University, Lyari, Karachi, Sindh, Pakistan

Received: 28 August 2025
Accepted: 04 October 2025

***Correspondence:**
Dr. Parisa Batul Ghulam Ali,
E-mail: drparisabatul@gmail.com

ABSTRACT

Deoxyribonucleic acid is not only responsible for normal functioning and metabolism of body by the formation of essential proteins which are responsible for individuals growth and development but it is also responsible for transferring traits & genetic disorders from parents to their offspring, either these genetic traits make them carriers or major diseased individual, these conditions may arise because of any false nucleotide base insertion, or nucleotide deletion or any gene replacement due to radiations or mutations. SMA (survival motor atrophy) is a condition that arises because of less production or unavailability of the SMN protein, which is synthesized by the SMN-1 gene. A case of 29 years old married woman (cousin marriage- Consanguinity) has been discussed, she lost her 4 babies after birth (neonatal deaths) in between the duration of 2 to 8 months, with one intrauterine miscarriage (intra-uterine death), after CVS it was found that SMN-1 was absent in the genetic makeup of her all babies, and they were not able to survive because of muscular atrophy in pulmonary muscles causing pulmonary distress and reduced body movements with edematous condition and other body organ failures including kidney and liver. It was concluded that SMN-1 gene absence is not only responsible for causing intrauterine, neonatal deaths but also causes sudden deaths in adult age suddenly by causing paralysis. Gene replacement therapies with other oligonucleotides and splicing modifiers have been introduced with the advancement of biotechnology for the treatment of SMA disease.

Keywords: Intra uterine deaths, Neonatal deaths, Spinal muscular atrophy, SMN-1 Gene, Genetic diseases

INTRODUCTION

Deoxyribonucleic acid is a sophisticated molecule that stores information necessary for organism creation and preservation. It serves as the fundamental unit of heredity in all organisms, defining the composition and functions of living things. Genetic disorders are conditions where the normal DNA sequence is altered, either completely or partially.[1,2] It can result from damage to chromosomes, mutations in one or more genes, multiple genes, or a combination of gene mutations and environmental factors. Over 6,000 recognized genetic disorders can be passed down from parents to offspring through genes, with conditions inherited according to various patterns.[3-5] Acquired mutations affect specific cells and cannot be passed on to offspring, leading to diseases like various cancers. These mutations alter genes controlling cell growth and DNA repair, causing abnormalities in cell function.[6] Lungs and skin cancers are often caused by multiple acquired mutations. Neurofibromatosis, a genetic disorder, can also result from acquired mutations during life.[7] Late-onset Alzheimer's Disease is influenced by genetics, environmental factors, and acquired mutations.[8]

Other multifactorial diseases like coronary artery disease, diabetes, and arthritis also involve gene-environmental interactions.[9-11] SMA is an autosomal recessive neuromuscular condition characterized by the loss of lower motor neurons.[12,13] It is a clinically variable disease, with types I, II, and III defined based on the onset and severity of symptoms. The International SMA Consortium has identified three clinical forms: SMA1, SMA2, and SMA3.[14] SMA-3 is further distinguished based on the age at onset and motor development milestones. Two

subgroups of type 3 SMA are SMA3a (onset before the age of 3) and SMA3b (onset at the age of 3).[15,16] Cases exhibiting initial illness signs between the ages of 20 and 30 are categorized as SMA.[4,12,17] The survival motor neuron (SMN) protein is not present in adequate amounts to protect motor neurons, leading to low levels of SMA in all its variants. Other SMA forms with atypical clinical signs, such as multiple contractures, bone fractures, or respiratory distress, have been defined as separate entities. Common symptoms include weakened muscles, reduced muscle tone, restricted movement, respiratory difficulties, challenges with eating and swallowing, slow development of gross motor skills, unprompted tongue motions, and spinal curvature.[18,19]

SMA is a genetically heterogeneous disease, with most classical cases being autosomal recessive due to deletions or mutations of the survival motor neuron gene 1 (SMN1) at the SMA 5q13 region. The SMN2 gene, located at this region, produces minor amounts of SMN protein, which plays a role in modulating the clinical phenotype of SMA. Patients with type I SMA have fewer SMN2 gene copies than those with types II and III. SMA plus types have different genetic traits, not linked to the SMA 5q13 region.20-22 The SMN protein is encoded by the two genes SMN1 and SMN2, with the SMN2 gene producing less SMN protein. The range of SMN2 copies in SMA patients is significantly greater, spanning from 1 to 6. The primary SMA phenotypic modulator is the amount of SMN2 copies. Some accounts suggest that the unusual asymptomatic biallelic deletion of the SMN1 gene may be caused by the presence of five SMN2 copies, compensating for the loss of both SMN1 gene alleles.[23]

The prevalence of SMA is estimated to be one case for every 7000–10,000 live births, resulting in one faulty gene for every 42–50 people. Recent studies suggest that 1 in 34 people may have a carrier state, indicating a higher prevalence. There is a great deal of phenotypic diversity in the disease, with the absence of the SMN1 gene being a significant factor in the prevalence rate.[24,25]

Schöneborn et al reported that 65 patients with SMA1 were diagnosed with SMA1 within the first six months of onset. Additionally, the number of SMN2 gene copies was detected and distinguished with findings of clinical-like heart abnormalities. Out of 65 patients, there were SMN2 genes in one copy in four patients, SMN2 genes in two copies in 56 patients, and SMN2 genes in three copies in five patients. Amongst these patients, 3 had inherited SMA along with atrial or ventricular septal defects.[26] Another study conducted in Guy's Hospital, London, examined during the neonatal period, finding decreased movements of the fetus in the middle of thirty and thirty-six weeks of gestation.[27] In France, SMN1 gene examination of SMA patients with types 1 to 3, which are 700 in number or more, was carried out from distinct geographic regions. There were 90 to 100% cases found in which the SMN1 gene was deleted homozygously.[28] In Singapore, molecular inspection was carried out on reserve DNA, and twenty-two patients had SMN1 gene homozygous deletion in exons 7 and 8.[29] Lochmüller et al estimated the overall prevalence of all SMA types, with 10 out of 100,000 live births.[30] Zhu et al reported that out of 40 SMA patients, 92.5% were homozygously deleted in exons 7 and 8, while 7.5% had only a deletion with exon 7 responsible for 7.5% of cases. No association was found between distinguished types of SMA and SMN1 gene deletion types of exons 7 and 8.[31]

In Morocco, a study was conducted on 54 patients, examining blood samples of peripheral veins from 54 patients and 30 control individuals. The DNA genome was obtained by applying processes that should be standardized, and the SMN1 gene was present in all individuals in the control category, but the SMN2 gene, both copies were absent in 10% of individuals, which do not play a role in clinical activities. There was a homozygous absence of the NAIP gene in exon 5 in 67% of SMA type I, 6/19 (32%) SMA type II, 1/19 (5%) SMA type III, and 2/10 (20%) SMA type IV patients. Due to the absence of the SMN1 gene, the absence of the NAIP gene was noted in patient.[32]

The objective of this case report is to explore how the absence of the SMN-1 gene leads to neonatal and intrauterine deaths. Additionally, the report aims to investigate whether the prevalence of this genetic condition is higher in neonates compared to adults.

CASE REPORT

A 29-year-old married woman (cousin marriage-Consanguinity) was brought to the secondary care hospital with a gestational age of 14 weeks, admitted for MTOP (Medical termination of pregnancy) due to a fetal gene defect, i.e., spinal muscular dystrophy. There are nine primary forms of muscular dystrophy, which is a genetic condition. Dystrophy is characterized as the process and outcome of inherited progressive affections of certain cells in one or more tissues that initially exhibit normal function.[33] Due to congenital anomaly (unusual or unexpected conditions in a baby's development during pregnancy), neonatal or intrauterine deaths increase.

Her gestational history was about G5 P3+1, which describes that first neonatal death reported after 8 months of survival, second neonatal death reported after 6 months of survival and third neonatal death reported after 4 months of survival, in fourth pregnancy miscarriage occurred and now in fifth pregnancy she was admitted in hospital for MTOP according to EIG classification by giving Misoprostol 200 mcg (3 tablets repeat after 3 hours). A placenta sample is taken as part of a prenatal test called chorionic villus sampling (CVS), which checks for chromosomal abnormalities and a few other genetic issues. The chorionic villi, which resemble small fingers made of placental tissue, are made of the same genetic material as the developing fetus. CVS is usually done between the 10th and 12th weeks of pregnancy. Her CVS report

indicates an absence of the SMN-1 Gene, it was an autosomal recessive genetic disorder. Her Beta HCG (human chorionic gonadotropin) level was about 1257.5; in men and non-pregnant or post-menopausal women, its level is around <10. Her blood group was O (+ve), and CBC findings report an Hb level of 11.5, Neutrophil count 60%, and she has no history of Hepatitis B & C. During the whole gestational age, liquor was adequate, and the yolk sac was noted, as shown in Figure 1.

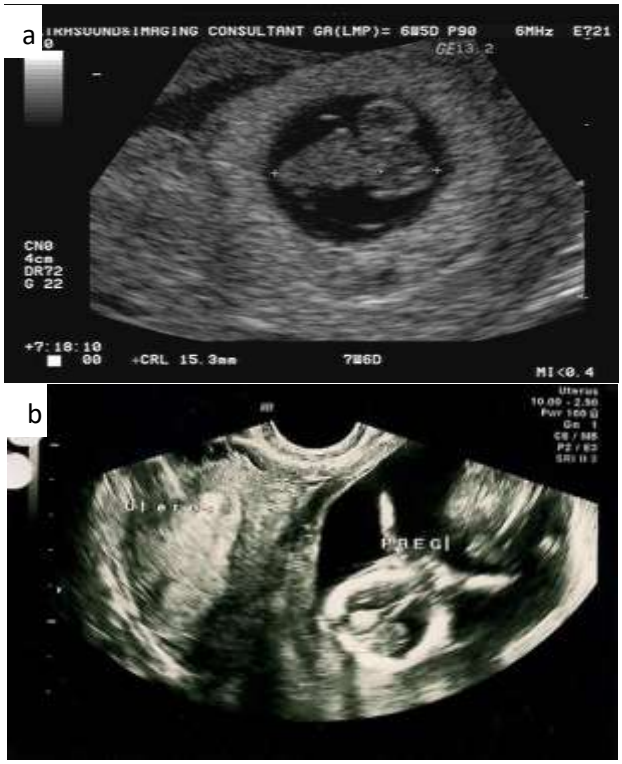

Figure 1: (a) Yolk sac at 7th weeks of gestational age (b) At 14th weeks of gestational age.

DISCUSSION

Deoxyribonucleic acid is responsible for conveying hereditary information from one generation to the next. It contains all phenotype and genotype characteristics, responsible for cycling traits from parents to offspring, including physical appearance, color, facial features, height, habits, likes, and dislikes. It also contains information that is responsible for making an individual a disease carrier or causing genetic deformities, which will lead to certain types of highly lethal conditions. Genetic diseases can be monogenic and multi-factorial; they result from gene displacement or addition of an abnormal amino acid (except essential amino acid), leading to abnormal sequencing and false proteins will produce and these conditions may arise due to fertilization between carriers (the prevalence rate is high in cousins' marriages).

In this study, a case of 29 years 29-year-old married woman was reported, who was admitted for MTOP. Behind pregnancy termination, there is a reason for the SMN-1 gene absence in the fetus, which was found after CVS. Her first three babies (neonates) also died after an interval of 8,6 and 4 months after birth, respectively. When she was expecting her 4th baby, a miscarriage was reported, and now in her 5th pregnancy, she went to MTOP. Mutation or biallelic deletion of Survival motor neuron, SMN protein at 5q13 region causes heterogeneous disease, i.e., Spinal Muscular Atrophy (SMA), which is an autosomal recessive disorder. In the above-described case report, due to muscular atrophy fetal movement decreases and it faces difficulty in contraction and relaxation of respiratory muscles, leading to respiratory distress, oxygen saturation in blood goes down, hypoxemic condition generated and oxygen supply to vital organs became compromised and caused intrauterine death at 14 months of gestational age, while in other cases this condition may cause severe organ damage or failure.

From the literature survey, it was found that the prevalence rate of SMA disease is equal in adults and children, and it affects all types of individuals. SMA disease is further classified into 3 main categories based on age group and severity. SMA-1 affects neonates within 6 months after birth, SMA-2 affects an individual within 8 months, while SMA-3 affects individuals of any age, causing weakness and making an individual unable to walk. It can be transferred from parents to children and, due to a mutation in the sequencing of the SMN protein, can suddenly affect muscular functioning. The above-discussed patient was not on any medical therapy for replacement or induction of genetic therapy to overcome this genetic condition. But with the advancement in science and technology, there are certain treatment options as well, which were designed to treat SMA caused by a mutation in the chromosome 5q13 region, leading to SMN protein deficiency. This therapeutic agent is named as Nusinnersin, i.e., Anti-sense oligonucleotide.[16,34] SMN-2 mRNA splicing modifiers are also designed to treat mutations in the 5q chromosome, named Risdiplam.[35] The goal of AAV-9-based therapy is to transfer a copy of the gene that codes for the human survival motor neuron (SMN) protein.[36] Nonpharmacological treatment, including physiotherapy, helps to strengthen patients' muscles and maintain their quality of life. Other options include whole body vibration and Scoliosis.[37,38]

CONCLUSION

It was concluded that SMA causes intrauterine and neonatal deaths (highly in cousin marriages), it also affects adults at any age and makes them unable to walk, causes respiratory distress, and vital organ failure, due to the absence of the SMN-1 gene. But this genetic condition can be treated by certain types of oligonucleotides, mRNA2 splicing modifiers, and induction therapy of genes by using biotechnological tools.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Park S, Jang SS, Lee S. Systematic analysis of inheritance pattern determination in genes that cause rare neurodevelopmental diseases. Front Gene. 2022;13:990015.
2. Leonardi E, Savojardo C, Minervini G. Molecular Effects of Mutations in Human Genetic Diseases. International J Mol Sci. 2022;23(12):6408.
3. Sciences NIoGM. What are the facts about genetic disease. 1974.
4. Wynbrandt J, Ludman MD. The encyclopedia of genetic disorders and birth defects. Infobase Publishing. 2010.
5. Kumar D. Introduction to Genes, Genome and Inheritance. Cardiovascular Genetics and Genomics: Principles and Clinical Practice. 2018:1-34.
6. Kent DG, Green AR. Order matters: the order of somatic mutations influences cancer evolution. Cold Spring Harbor perspectives in medicine. 2017;7(4):27060.
7. Larsen JE, Minna JD. Molecular biology of lung cancer: clinical implications. Clinics in chest Med. 2011;32(4):703.
8. Rabinovici GD. Late-onset Alzheimer disease. Continuum: Lifelong Learning in Neurology. 2019;25(1):14-33.
9. Humphries SE, Montgomery HE, Talmud PJ. Predisposing genes, high-risk environments and coronary artery disease: LPL and fibrinogen as examples. World Rev Nutr Diet. 2001;89:61-7.
10. Szalai C. 12. Gene environmental interaction.
11. Kwabi-Addo B, Kwabi-Addo B. Gene-Environment Interactions in Health Disparities. Health Outcomes in a Foreign Land: A Role for Epigenomic and Environmental Interaction. 2017:233-277.
12. D'Amico A, Mercuri E, Tiziano FD, et al. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:1-10.
13. Mercuri E, Sumner CJ, Muntoni F. Spinal muscular atrophy. Nature Rev Dis Prim. 2022;8(1):52.
14. Salort-Campana E, Quijano-Roy S. Clinical features of spinal muscular atrophy (SMA) type 3 (Kugelberg-Welander disease). Archives de Pédiatrie. 2020;27(7):723-8.
15. Lupica A. Evaluation of disease progression and response to therapy in a cohort of late childhood/adulthood SMA patients: Is there room for new markers. 2023.
16. Coratti G, Cutrona C, Pera MC. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis. 2021;16:1-12.
17. Souza PVS, Pinto W, Ricarte A. Clinical and radiological profile of patients with spinal muscular atrophy type 4. European J Neurol. 2021;28(2):609-19.
18. 18. Chaytow H, Huang Y-T, Gillingwater TH. The role of survival motor neuron protein (SMN) in protein homeostasis. Cell Molec Life Sci. 2018;75:3877-94.
19. Coovert DD, Le TT, McAndrew PE. The survival motor neuron protein in spinal muscular atrophy. Human Molec Gen. 1997;6(8):1205-14.
20. 20. Garcia-Cabezas M, Garcia-Alix A, Martin Y. Neonatal spinal muscular atrophy with multiple contractures, bone fractures, respiratory insufficiency and 5q13 deletion. Acta Neuropathologica. 2004;107:475-8.
21. MacKenzie A, Jacob P, Surh L, et al. Genetic heterogeneity in spinal muscular atrophy: A linkage analysis-based assessment. Neurology. 1994;44(5):919.
22. Gilliam T, Brzustowicz L, Castilla L, et al. Genetic homogeneity between acute and chronic forms of spinal muscular atrophy. Nature. 1990;345(6278):823-5.
23. Boda B, Mas C, Giudicelli C. Survival motor neuron SMN1 and SMN2 gene promoters: identical sequences and differential expression in neurons and non-neuronal cells. European J Human Gen. 2004;12(9):729-37.
24. Coratti G, Ricci M, Capasso A, et al. Prevalence of spinal muscular atrophy in the era of disease-modifying therapies: an Italian Nationwide Survey. Neurology. 2023;100(11):522-8.
25. Belter L, Taylor JL, Jorgensen E. Newborn screening and birth prevalence for spinal muscular atrophy in the US. JAMA pediatrics. 2024;178(9):946-9.
26. Rudnik-Schöneborn S, Heller R, Berg C. Congenital heart disease is a feature of severe infantile spinal muscular atrophy. J Med Gen. 2008;45(10):635-8.
27. Macleod MJ, Taylor JE, Lunt PW. Prenatal onset spinal muscular atrophy. European J Paediat Neurol. 1999;3(2):65-72.
28. Schmalbruch H, Haase G. Spinal muscular atrophy: present state. Brain Pathol. 2001;11(2):231-47.
29. Lai A, Tan E, Law H, et al. SMN1 deletions among Singaporean patients with spinal muscular atrophy. Ann Acad Med Singapore. 2005;34(1):73-7.
30. Verhaart IE, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy–a literature review. Orphanet journal of rare diseases. 2017;12:1-15.
31. Zhang Y, He J, Zhang Y. The analysis of the association between the copy numbers of survival motor neuron gene 2 and neuronal apoptosis inhibitory protein genes and the clinical phenotypes in 40 patients with spinal muscular atrophy: Observational study. Medicine. 2020;99(3):18809.
32. Bouhouche A, Benomar A, Birouk N. High incidence of SMN1 gene deletion in Moroccan adult-onset spinal muscular atrophy patients. J Neurol. 2003;250:1209-13.
33. Rall S, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myologica. 2012;31(2):117.
34. Claborn MK, Stevens DL, Walker CK. Nusinersen: a treatment for spinal muscular atrophy. Annals of Pharmacotherapy. 2019;53(1):61-9.

35. Kakazu J, Walker NL, Babin KC. Risdiplam for the use of spinal muscular atrophy. Orthopedic Reviews. 2021;13(2):25579.
36. Mahajan R. Onasemnogene abeparvovec for spinal muscular atrophy: the costlier drug ever. Medknow. 2019: 127-8.
37. Dutt V, Gupta S, Dabur R. Skeletal muscle atrophy: Potential therapeutic agents and their mechanisms of action. Pharmacological Res. 2015;99:86-100.
38. Rad N, Cai H, Weiss MD. Management of spinal muscular atrophy in the adult population. Muscle & Nerve. 2022;65(5):498-507.

Cite this article as: Ali PBG. Homozygous SMN1 gene deletion as a cause of intrauterine and neonatal mortality. Int J Reprod Contracept Obstet Gynecol 2025;14:4004-8.