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Case Report *Volume 6 Issue 1*

Previous Two Children Affected with Spinal Muscular Atrophy with Only One Parent Screened Positive for Carrier Status; Dilemmas in Prenatal Diagnosis

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Abstract

Background: Spinal muscular atrophy is a genetically heterogenous disorder, mostly having a recessive inheritance. If the child is diagnosed with this genetic disease, parental screening for spinal muscular atrophy is recommended before planning for future pregnancy as interpreting the results of carrier screening in the context of family history can be challenging.

Case: We report the case of a 28-year-old woman with two previous children affected with SMA type 1 succumbed at the age of 6 months; and husband with negative carrier status. Exome sequencing of affected child showed no point mutations. Multiplex ligation probe amplification (MLPA) showed homozygous deletion of both the copies of SMN1 gene. Mother was carrier as her test revealed single copy of SMN1 gene whereas father appeared to be non-carrier with presence of two copies of the same gene. Diagnostic testing for the fetus for SMA showed two copies. Father could be a silent carrier for SMA having cis configuration.

Conclusion: Interpretation of carrier screening results could be challenging in case of one of the parents carrying cis configuration and thus behaving as a silent carrier. In these situations, additional genetic testing and genetic counseling are indicated to clarify risk for SMA in pregnancy and guide prenatal diagnosis.

Keywords: Carrier Screening; Spinal Muscular Atrophy; Prenatal Diagnosis; Genetic Testing

Abbreviations

MLPA: Multiplex Ligation Probe Amplification; SMA: Spinal Muscular Atrophy; PCR: Polymerase Chain Reaction.

Introduction

Spinal muscular atrophy (SMA) is a genetically heterogeneous disease, primarily inherited in an autosomal recessive manner [1,2]. Clinically, it is characterized by the progressive degeneration of motor neurons in the anterior horn of the spinal cord, leading to hypotonia, muscle atrophy, paralysis, and, in severe cases, death [3,4]. The incidence is approximately 1 in 10,000 live births, with a carrier frequency of 1/40–1/60 [5,6]. SMA is categorized into four clinical subtypes based on the age of onset and clinical severity.

The survival motor neuron (SMN) gene determines SMA and is located on the 5q 11.2–13.3 region, with two homologous copies: SMN1 and SMN2, the latter being a nearly identical copy of the SMN1 gene [7]. The most common mutation in SMA patients involves the homozygous

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deletion of exons 7 and 8 of SMN1, accounting for over 95% of cases. However, approximately 5% of patients present as compound heterozygotes, having only one deletion of SMN1 and intragenic gene mutations, such as missense, nonsense, frameshift, and splice-site variations, on the other chromosome [6]. Diagnostic methods include PCR-RFLP assay or MLPA, with MLPA currently considered the gold standard for detecting homozygous deletions of the SMN1 gene [8].

Case Report

A couple sought genetic consultation and prenatal diagnosis after their two previous children were diagnosed with SMA (Figure 1). Despite being in a non-consanguineous marriage, the second child, upon investigation, showed no deletion on PCR analysis for the SMN gene, and exome sequencing revealed no mutations. Subsequently, MLPA testing identified a homozygous deletion in the SMN1 gene (exon 7 and exon 8) (Figure 2).

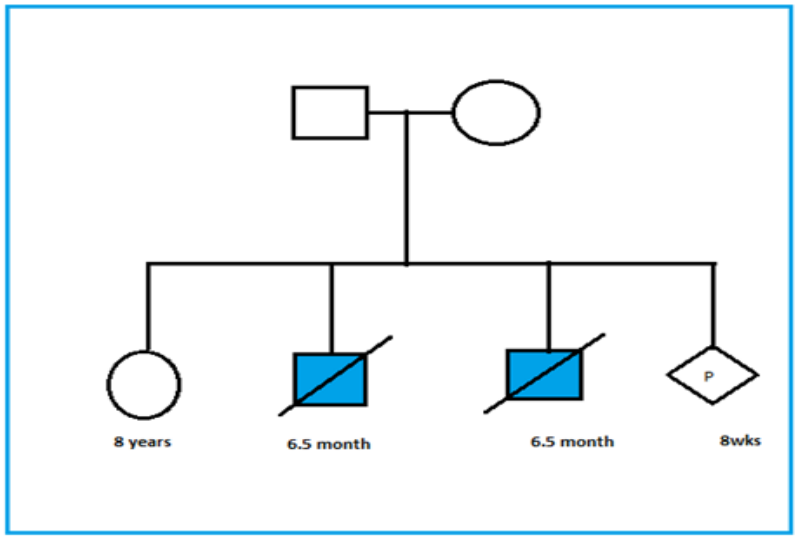

Figure 1: Pedigree showing affected family members and carriers of SMA.

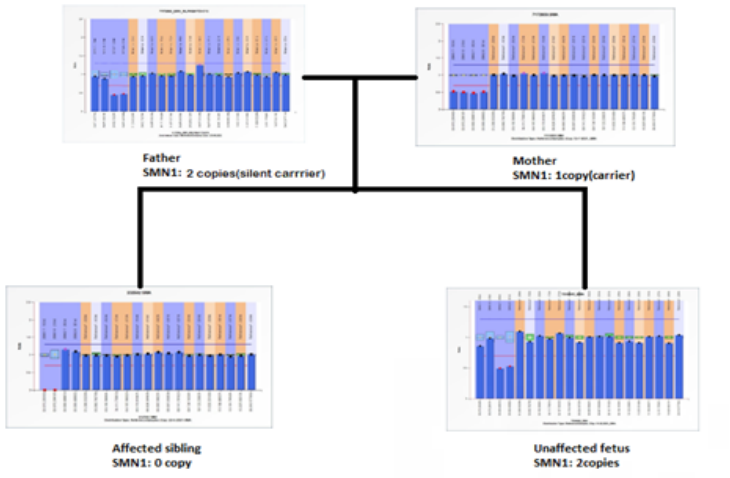

Figure 2: MLPA graph image of a) Father; b) Mother; c) Index case; and d) Fetus.

The index case displayed a homozygous deletion in the SMN1 gene (exon 7 & 8). Segregation analysis revealed the mother as a heterozygous carrier for the deletion in SMN1 gene (exon 7 & 8) and SMN2 gene. The father showed no deletion in the SMN1 gene but had a heterozygous deletion in the SMN2 gene which is of no significance.

The couple was referred for prenatal diagnosis and genetic counseling. Chorionic villus sampling (CVS) was performed at 12 weeks, and FISH ruled out common chromosomal aneuploidies (chromosomes 13, 18, 21, X, and Y), revealing aneuploidy in the sex chromosome (45,XO). Amniocentesis was recommended to exclude the possibility of confined placental mosaicism (CPM). Amniocentesis at 16 weeks showed no aneuploidy in the five chromosomes tested. Mutation study from amniotic fluid revealed a normal karyotype (46,XY) and the presence of 2 copies of the SMN1 gene, leading to the decision to continue the pregnancy (Figure 2). A healthy child was delivered at full term.

Discussion

The diagnosis of SMA requires identifying biallelic pathogenic variants in SMN1 for a proband with a history of motor difficulties or regression, proximal muscle weakness, reduced/absent deep tendon reflexes, and evidence of motor unit disease. The SMN1 gene encodes the survival motor neuron protein, crucial for maintaining motor neurons that facilitate communication between the central nervous system and skeletal muscles. While over 96% of SMA cases result from homozygous deletions of exons 7 and 8 of SMN1, about 4% are due to point mutations detectable through gene sequencing [9].

SMA is inherited in an autosomal recessive manner, usually from carrier parents, with approximately 2% of cases attributed to de novo events [10]. Carriers may have one working copy of SMN1 or two copies in a cis configuration (Figure 3). Standard carrier screening for SMA is dosage-based, determining the number of SMN1 copies. The phase is estimated through a single nucleotide polymorphism (SNP), g.27134 T > G, correlated to cis configuration and an increased risk of silent carrier status [11] (Figure 1). Utilizing SNP data in carrier screening can help assess the risk for silent carrier status, though its accuracy is limited to specific ethnic groups [6].

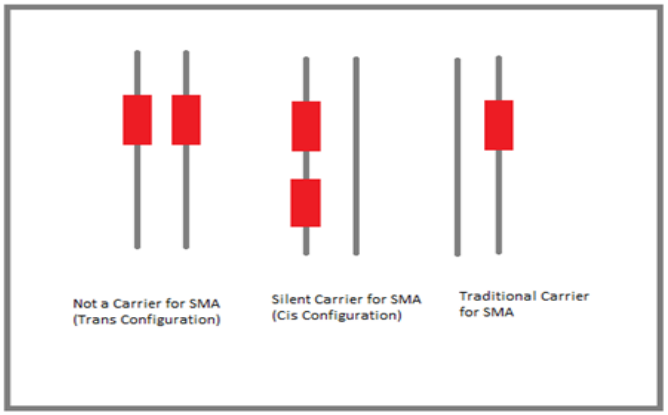

Figure 3: Phase configurations of SMN1 copies.

If SMN gene analysis reveals 3 copies of SMN1 in an offspring, it suggests that one parent is a silent carrier contributing 2 copies, while the other is not a silent carrier contributing 1 copy. However, if two copies are found in one parent, SNP analysis is required to determine whether copies are in cis configuration and the patient is a silent carrier. If the individual carries the SNP, they are reported as being at "increased risk to be a carrier," but true silent carrier status requires linkage studies. Testing additional family members of the parent with the [2+0] SMN1 genotype may provide informative results, as usually, one of their parents has a deletion (1/0 SMN1 genotype), and the other parent has three or more SMN1 copies (2/1 SMN1 genotype). If the parent with the [2+0] SMN1 genotype has children with another parent who is a known carrier, the children are at a 25% risk of having SMA in every pregnancy.

In our case, the father was a silent carrier, while the mother was a known carrier. Although there are high chances of missing the silent carrier in such cases, the presence of two affected children with SMA raised suspicion, leading to the recommendation for prenatal diagnosis. Genetic testing for common chromosomal aneuploidy should be conducted whenever an invasive procedure is performed for a single gene disorder. If ambiguity arises in chorionic villus sampling results, verification through repeating the test from an amniotic fluid sample is essential.

In conclusion, this case underscores important considerations when interpreting test results from carrier screening, emphasizing the significance of family history data and recognizing the limitations of the testing process. Carrier screening results are not diagnostic but only estimate the risk for carrier status. Due to the complexity of SMA and the

limitations of screening, patient results must be reviewed considering family and medical history before proceeding with prenatal diagnosis. Referral to a genetic counselor or genetics specialist is advisable when a history suggests carrier status inconsistent with genetic screening. The establishment of a national program for carrier screening is recommended as a preventive disease strategy.

Declaration

Ethics approval and consent to Participate

Ethical clearance for this study was exempted

Consent for Publication

Written informed consent was obtained from the parents of the patient for this publication.

Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

"The authors declare no conflict of interest."

Funding

NIL

Authors' Contributions

KP and RA conceived of the presented idea and designed the study. KP performed the examination, evaluated the reports, and verified the analytical methods. RA encouraged KP to investigate and supervised the findings of this work. KP and HP designed the figures. KP interpreted the results and worked on the manuscript. All authors discussed the results and contributed to the writing of the manuscript.

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References

1. Jiang W, Ji X, Xu X, Qu X, Sun W, et al. (2013) Molecular prenatal diagnosis of autosomal recessive spinal muscular atrophies using quantification polymerase chain reaction. Genet Test Mol Biomarkers 17(5): 438-442.

2. Reardon LB, Sacharow S, Ahearn ME (1993) Spinal Muscular Atrophy, X-Linked Infantile. GeneReview.

3. Hasanzad M, Golkar Z, Kariminejad R, Hadavi V, Almadaniet N, et al. (2009) Deletions in the survival motor neuron gene in Iranian patients with spinal muscular atrophy. Ann Acad Med Singapore 38(2): 139-141.

4. Omrani O, Bonyadi M, Barzgar M (2009) Molecular analysis of the SMN and NAIP genes in Iranian spinal muscular atrophy patients. Pediatr Int 51(2): 193-196.

5. Markowitz JA, Singh P, Darras BT (2012) Spinal muscular atrophy: a clinical and research update. Pediatr Neurol 46(1): 1-12.

6. Kocheva SA, Karanfilska DP, Trivodalieva S, Kuturec M, Jekicet SV, et al. (2008) Prenatal diagnosis of spinal muscular atrophy in Macedonian families. Genet Test 12(3): 391-393.

7. Dhamcharee V, Mutirangura A, Tannirandom Y, Jongpiputvanich S, Romyananet O (1999) Prenatal prediction of spinal muscular atrophy by SMN deletion analysis. Southeast Asian. J Trop Med Public Health 2: 186-187.

8. Hassan HA, Fahmy NA, Bagoury ENM, Eissa NR, Wessam E, et al. (2022) MLPA analysis for molecular diagnosis of spinal muscular atrophy and correlation of 5q13.2 genes with disease phenotype in Egyptian patients. Egypt J Med Hum Genet 23: 156.

9. Lunn MR, Wang CH (2008) Spinal muscular atrophy. Lancet 371(9630): 2120-2133.

10. Wirth B, Schmidt T, Hahnen E, Schoneborn SR, Krawczak M, et al. (1997) De novo rearrangements found in 2% of index patients with spinal muscular atrophy: mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling. Am J Hum Genet 61(5): 1102-1111.

11. Luo M, Liu L, Peter I, Zhu J, Scott SA, et al. (2014) An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med 16 (2): 149-156.