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CASE REPORT

Duchenne Muscular Dystrophy: Carrier Discretion to Prenatal Care—Report of a Case

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ABSTRACT

Duchenne muscular dystrophy (DMD) is the most common hereditary cause of neuromuscular weakness and the most common of X-linked recessive diseases. It is caused by a mutation in the DMD gene located on chromosome X, 21.2 locus that encodes the dystrophin protein. Nucleic acid analytical techniques have advanced so much that the identification of potential carriers is possible by assessment of the causative mutations. The following case report describes the identification of a *denovo* dystrophin gene mutation in a carrier female and the subsequent antenatal workup of her present pregnancy

Keywords: Duchenne muscular dystrophy, Prenatal diagnosis, Amniocentesis

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common hereditary cause of neuromuscular weakness and the commonest of X linked recessive diseases.[1] Preconceptional and prenatal diagnosis of this condition is a challenge in modern medical practice which is tried to be explored in this article.

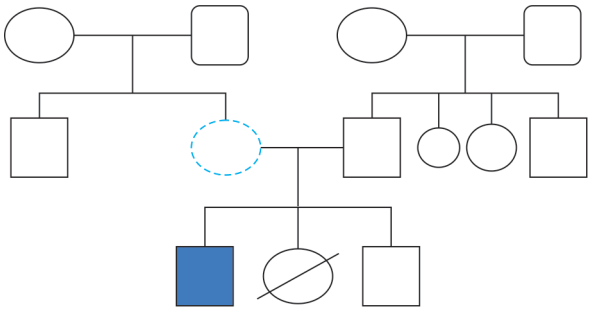
CASE REPORT

A 33-year-old female presented with the intention to conceive soon. She has a son who developed features of neuromuscular dysfunction characterized by frequent falls and proximal muscle weakness from 3 years of age onwards. She wanted to know how to prevent the condition in her next child. She was advised to do genetic analysis of her son and depending upon the transmission pattern of the child's diagnosis, measures such as preimplantation genetic diagnosis to choose the normal embryo for implantation, or if not amenable to that, donor gamete reproduction was advised. She came back to us as G3P1L1A1 with 6 weeks of gestation, spontaneous conception for antenatal care. Her first son is of 8 years old and has been diagnosed to have Duchenne Muscular Dystrophy. DNA tested for dosage analysis of 79 exons of the dystrophin gene showed duplication in the dystrophin gene involving exon 46. The same test performed on maternal DNA showed a heterozygous duplication in the dystrophin gene involving exon 46. This suggested that the mother is an asymptomatic case of dystrophin gene deletion and hence a carrier of Duchenne muscular dystrophy. There is no history of neuromuscular disorders in her family, intuiting the possibility of a denovo dystrophin gene mutation in the subject. Amniocentesis was performed at 16 weeks of gestation. Genomic DNA of the amniotic fluid was analyzed for the dosage of various exons of the dystrophin gene, including exon 46 which was duplicated in the elder affected child. Results indicate that the fetus is not likely to be affected with DMD.

DISCUSSION

Duchenne muscular dystrophy (DMD) is the most common hereditary cause of neuromuscular weakness

Pedigree Chart



The pedigree chart shows three generations – 1st level – is the grandparents level who were all normal with respect to dystrophin genes. 2nd level – the parental generation – shows a denovo carrier mutation in the mother and a normal father. The brother of the mother is also normal. The 3rd level is that of the present generation – shows an affected male child who has inherited the X-linked recessive mutation from his mother and has become affected with Duchenne muscular dystrophy. There is also a spontaneous expulsion of a female fetus in this family. The third child has been evaluated for dystrophin gene mutation by means of fetal cells obtained by amniocentesis and has been shown to be free of dystrophin gene mutation, suggestive of a mosaic pattern of dystrophin gene mutation in the carrier mother

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and the most common X-linked recessive disease.[1] It is a progressive myopathy characterized by muscle weakness and degeneration. Symptoms start around 3 years of age and weakness progresses from hip girdle muscles and neck flexors to shoulder girdle muscles and then proceeds distally. Hypertrophied calf muscles and Gower's maneuver wherein the child perform a sequence of movements akin to climbing upon himself, in order to stand up are characteristic of the disorder. Dystrophin protein is also present in the brain, explaining the mild mental handicap which often goes along with the myopathy. Victims succumb to respiratory or cardiac failure early in life.

Both DMD and Becker's muscular dystrophy (a milder variant of the same) are caused by mutations in the DMD gene located on chromosome X, 21.2 that encodes dystrophin protein. DMD gene is also credited to be the largest human gene, containing 79 exons.[2] Mutations in this large gene cause either a change in reading frame (frameshift mutation) or a premature stop codon. The dystrophin protein connects the action of the contractile unit to the connective tissue that envelops the sarcomere. A defect in this protein disrupts the connection between the actin of cytoskeletal unit to connective tissue and results in muscle fiber dysfunction. Damaged muscle gets replaced by fibrous tissue and fat.[2]

There is a high rate of mutation in the DMD gene. Common mutations include deletions (~ 68%) especially between exons 45 and 55 and duplications (~ 11%), between exons 2 and 10 and other minor mutations (~20%). Undetected mutations account for approximately 2% cases. The impact of deletions and duplications depends upon whether the number of nucleotides changed is divisible by 3, if so, the reading frame will not be shifted.[3]

Carrier females are often clinically normal, though, in less than 5% of cases, clinical manifestations do occur.[4] Carrier females can also transmit the disease by means of germline mutations. Since the disease is inherited in X-linked recessive pattern, 50% of daughters will be carriers and 50% of sons will be affected. An affected male will transmit carrier state to all daughters and does not transmit to sons. A full-blown case of DMD often does not live up to reproductive age while a milder case of Becker's might reproduce.

Nucleic acid analyses have advanced so much that the identification of potential carriers is possible by assessment of the causative mutations. Still, risk assessment by genetic counseling of carriers is challenged by the wide variety of plausible mutations.

Preimplantation genetic diagnosis can be employed to identify the embryo carrying the potential mutation. This can prevent the requirement of selective termination of pregnancy. Whole genome amplification is an essential step for preimplantation genetic diagnosis.

Multiple displacement amplification (MDA) works on bacteriophage F29 DNA polymerase to amplify the whole genome of single cells. MDA has also been used for preimplantation genetic diagnosis of beta-thalassemia, cystic fibrosis, Marfan syndrome, fragile X syndrome, and X-linked adrenoleukodystrophy.[5,6]

Denovo mutations arising at the grandparent level can ordain carrier state among the parental generation of the affected child. Hence the diagnosis of this condition in a child warrants genetic analysis for the gene mutation, not only among parents but also among close female relatives of the mother. This, in turn, can prevent the birth of another affected child in the family. During the antenatal period, testing of chorionic villus samples/amniocentesis obtained fetal sample can make the diagnosis possible. Maternal plasma-derived fetal DNA can be subjected to a custom solution based target enrichment designed to cover the entire dystrophin gene region.[7] Assessment of creatinine phosphokinase levels in a fetal blood sample can help assess the severity of the phenotype.

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