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Mutational Analysis in Dystrophin Gene with Dystrophinopathy: A Novel Familial Case Report in Tamil Nadu

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ABSTRACT Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular degenerative disorder initiated by mutation in the dystrophin gene that is located on chromosome Xp21.The present case is a novel report of DMD with co-occurrence of Autism associated disorder, which has a similar genetic component. In this report, the researchers present a family based study of a 17 year old male who has been diagnosed with DMD. The objective of the present case report is to identify the genetic abnormalities of the DMD gene and associated neuro behavioral disabilities. The methodology of the study followed classical cytogenetic techniques in which genetic alterations showed deletion of exon 45 in chromosome Xp21.2. From this case study, the researchers report that, the mother is a carrier for transmitting DMD to her male offspring.

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is a rare X-linked recessive genetic disorder among the dystrophinopathy spectrum, mainly caused by the mutation in the dystrophin gene (Monaco et al. 1985). The prevalence of DMD is about 1 in 3500, common among male children (Monckton et al. 1982) and the onset is before 3 years of age. DMD gene consists of 79 exons (Den et al. 1989) and has 2.5 million base pairs. Dystrophin is the protein coded by DMD, which plays a vital role in muscle tissues and cell signaling. Point mutations, duplication and large deletion occurs between exons 45-47. Females are carriers for this disease, while males are the affected individuals. The carrier mother will pass a defective gene by a chance of 50 percent to the son as well as to the daughter. The unaffected father can pass normal X to his daughter or normal Y to his son. The clinical hallmarks include early start with advancing muscle weakness. Researches have also noted an increased risk for intellectual disability (MR) and autism among individuals with DMD. Children with DMD are commonly seen with difficulty in walking, underdeveloped motor skills, fatigue, calf hypertrophy, respiratory problems (Sakthivel 2013), positive Gower's sign and Pradhan's valley sign (Emery 1991). Normally, 20 percent of DMD patients will die due to cardiac failure (Simonds et al. 2002).

There is evidence that the framework of the central nervous system (CNS) is altered among the males with DMD (Anderson et al. 2002) as well as cardiac muscles. In CNS, dystrophin play a vital role (Uchino et al. 1994), but in the case of DMD, there is a deficiency of dystrophin in cerebrum and cerebellum (Hendriksen and Vles 2008). About one-third of males exhibit the signs of mental retardation, dyslexia, inability in motor tasks and other associated functions thought to rely on the cerebellum (Hendriksen and Vles 2006). Till then, only a few studies have demonstrated the incidence of neuropsychiatric disorder in a population of DMD (Joseph Hendriksen

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and Vles 2008). A review article explained the development of cognitive and behavioral abnormalities increased the frequency of autism and attention deficit disorders in DMD cases (Mehler 2000). The dystrophin glycoprotein complex (DGC) is a major component of dystrophin, plays a vital role in cardiac muscles, by disrupting and causing muscle membrane fragility and increasing the susceptibility to mechanical stress. This process initiates muscle necrosis and degeneration in both skeletal and cardiac muscles (Ozawa et al. 1990) and there are some other reports that have failed to explain the mechanism of dystrophin in cardiac muscles. Generally, cardiomyopathy is seen in Becker muscular dystrophy, but in rare cases it can be observed in DMD (Yazawa et al. 1987). X-linked dilated cardiomyopathy (XLDCM) is a congestive heart failure due to dilated cardiomyopathy (DCM), seen in individuals aged from 10-20 years and slow progression of DCM is seen in females between 40-50 years of age.

In order to provide appropriate diagnostic criteria for DMD, molecular genetic analysis is an important underlying platform for detecting the mode of inheritance in dystrophinopathy. In DMD, deletion of one or more exons can counterpart 65 percent, whereas duplications accounting for 6-10 percent, while in DCM the genetic alterations are seen with deletion in exons 45-51 (Arbustini et al. 2000). The biomarker, serum creatine kinase shows both specificity and sensitivity for accurate prediction of the dystrophinopathy. DMD can be diagnosed by performing muscle biopsy, genetic testing, biochemical tests and electromyography.

This study reports a case of a 17 year old boy from Tamil Nadu, India, diagnosed with DMD also had a family history of DCM and ASD.

CASE INVESTIGATION

A 17 year old male diagnosed with DMD has been referred to our department for genetic studies. The study has been carried out from 2014 to July 2016 and the patient was followed up. The family history has been studied thoroughly and pedigree analysis was performed. As per the history, it was noted that, his elder sister passed away at the age of 20, had severe autistic features and was mentally challenged. Similarly, one of the kinsman also died at the age of 36 due to DCM, which showed that it might have been genetically inherited where his mother was a carrier of DMD and DCM. The indexed patient was mentally challenged with mild autistic features and the intelligence quotient (IQ) level was low. The case has been presented with fatigue, deformities of chest and the back, bone deformities and defects in motor skills. There were no serious respiratory or cardiac complications. He was advised to take phenytoin and quinine for muscle relaxation. Before the diagnosis of DMD, he was advised to take corticosteroids and DMD was noted when he was 5 years old. Presently, multivitamin supplements were prescribed for him. Genetic analyses were carried out using peripheral blood which showed deletion in chromosome Xp21.2 and PCR-RFLP results confirmed the deletion of exon 45.

OBSERVATIONS AND DISCUSSION

Molecular diagnosis confirmed deletion in exon 45 and chromosomal abnormalities revealed deletion in Xp21.2. From the questionnaire and family history, it has been detected that his mother was a carrier, his sister died due to cardiac failure at the age of 20, as a child he had difficulty in walking and was mentally retarded. From the family history his sister had autistic features as well as cardiomyopathy and one of the kinsman died due to heart disease at the age of 36, might have had cardiomyopathy. Cardiomyopathy is associated with DMD in some cases. The inheritance of DCM in DMD is very rare, since cardiac failure occurs during the fifth decade in Becker muscular dystrophy (Bushby et al. 2003). Genetic testing has revealed that the mutation in DMD causes inability to synthesize dystrophin which is essential for muscle contraction (Suneja et al. 2015). In the present case, chromosomal analysis reports a deletion on Xp21.2 and mutational studies has shown deletion of exon 45 which coincides with two cases already reported from India (Rathod et al. 2014; Suneja et al. 2015).

From the case history the patient had severe DMD associated with mental retardation. Thus, the researchers concluded that the elder sibling of the patient had severe autistic features; his mother was a carrier who might have transmitted the disease, in which the daughter had a recessive condition of DMD. This was similar to previously reported other three studies that

showed an association between DMD and autism spectrum disorders (Wu et al. 2005; Dark et al. 2006; Komoto et al. 1984). At present, mortality and quality of life of DMD patients has been improved through medication with corticosteroids and physiotherapy which lessen the progress of muscle weakness. Genetic testing is mandatory if the family history is present or not. To our knowledge, this is the first familial report of DMD associated with autistic features and cardiomyopathy reported from the state of Tamil Nadu, India.

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