



Original Research

Muscular Dystrophy: A Retrospective Evaluation of 15 Cases

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Abstract

Objectives: The aim of this study was to investigate the clinical and laboratory findings of patients followed up with a diagnosis of Duchenne muscular dystrophy (DMD).

Methods: This retrospective study included 15 boys diagnosed with muscular dystrophy at the Pediatric Neurology Department between July 2008 and July 2016. The presenting symptoms; level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine kinase (CK); ophthalmological findings; echocardiography (ECHO) results; findings on brain magnetic resonance imaging (MRI); genetic analysis results; and muscular biopsy findings were evaluated.

Results: The mean age of the patients was 5.2 ± 2.3 years (range: 11 months-8 years) and the mean age at the onset of DMD was 4.1 ± 2.2 years (range: 10 months-6 years). The ALT level ranged between 67 and 527 IU/L, the AST between 44 and 455 IU/L, and the CK between 931 and 19,595 IU/L. The genetic analysis determined deletions in 12 (80%) and duplications in 2 (13%) patients.

Conclusion: Parents with a DMD-affected child should be provided with genetic counseling in order to make decisions about future pregnancies.

Keywords: Child; genotype; muscular dystrophy.

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Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy, with a reported incidence of 1 in 3,500 live male births.^[1] DMD is the result of gene mutations, deletions or duplications that cause a loss of function in the dystrophin gene on the X chromosome. The symptoms of DMD typically start before the age of 5 years. Children with DMD have difficulty running, jumping, and climbing stairs due to the involvement of the proximal muscle. They often use their hands to support the body when rising to a standing position from the floor or a chair (Gowers' sign). Children with DMD aged 5 years or less have a creatine kinase (CK) level that is 10 to 200 times greater than normal. Most patients die in their 20s due to cardiac

failure and infection. Over time, cardiomyopathy develops in one-third of DMD patients. The standard treatment for DMD includes the use of corticosteroids and ataluren.^[2-4] The aim of this study was to investigate the clinical and laboratory findings of patients followed up with a diagnosis of DMD.

Methods

This retrospective study included 15 boys who were diagnosed with DMD at the Pediatric Neurology Department between July 2008 and July 2016. The diagnosis was established based on clinical signs and symptoms, serum CK measurements, genetic tests, and muscular biopsy find-

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ings. The presenting symptoms, parental consanguinity, neurological symptoms, genetic analysis findings, and the prognosis of the disease were recorded for each patient. An evaluation was made of brain magnetic resonance imaging (MRI) findings, ophthalmological findings, ECHO results, muscular biopsy findings, and the level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and CK. Mutations in the dystrophin gene were primarily identified using the multiplex ligation-dependent probe amplification (MLPA) method (SALSA MLPA probemix P034-A3/P035-A3 DMD/Becker; MRC-Holland, Amsterdam, Netherlands), which enables the detection of deletions or duplications in all 79 exons. The data obtained were analyzed using Coffalyser MLPA analysis software (MRC-Holland, Amsterdam, Netherlands). For single exon deletion, further verification was performed with polymerase chain reaction (PCR) analysis and sequencing.^[5] The study was approved by the Ethics Committee. Informed consent was obtained from the parents of all the children.

Results

The 15 patients had a mean age of 5.2 ± 2.3 years (range: 11 months-8 years). The mean age at the onset of DMD was 4.1 ± 2.2 years (range: 10 months-6 years). On physical examination, all of the children were within the normal percentiles for height, body weight, and head circumference. The parents of 2 (13%) children had second-degree consanguinity. Three (20%) children had a family history of DMD. MRI examination was performed on 5 (33%) children and the findings were normal. One (7%) child had epilepsy and was on antiepileptic treatment. Mild mental retarda-

tion was detected in 1 (7%) patient. In all of the patients, pseudohypertrophy was detected in the gastrocnemius muscle. Ten (67%) children were on steroid treatment. Two (13%) children had mild dilated cardiomyopathy. Three (20%) patients had difficulty walking (Table 1). The ALT level ranged between 67 and 527 IU/L, the AST level between 44 and 455 IU/L, and the CK level between 931 and 19.595 IU/L. A genetic analysis was performed for each patient. The cases with no mutation identified on MLPA and denaturing high performance liquid chromatography were diagnosed as DMD on the basis of muscle biopsy indicating the absence of dystrophin expression and on clinical manifestations. Deletions were detected in the genetic analysis of 12 (80%) patients, and duplications in 2 (13%) patients (Table 2). In 1 patient, the genetic analysis result was negative; however, a muscle biopsy revealed a myopathic change (necrotic and regenerative muscle fibers) and the diagnosis was made based on the examination findings.

Table 1. Walking capability, medications, and intervention in the participants with Duchenne

Clinical Features	n (%)
Walking capability	
Normal walking	12 (80)
Not able to walk	3 (20)
Cardiac function	
Dysfunction	3 (20)
Normal	12 (80)
Steroid treatment	
Yes	10 (66.6)
No	5 (33.3)

Table 2. Confirmed point mutations, small deletion/insertion of Duchenne muscular dystrophy/Becker muscular dystrophy patients

No.	Gender	Years	Phenotype	Family history	Exon/Intron	AST	ALT	CK
1	M	6	DMD	-	8-17	125	97	11234
2	M	11 months	DMD	+	45-50	527	234	9876
3	M	3	DMD	-	45-52	98	128	16400
4	M	8	DMD	-	45-52	305	203	12300
5	M	7	DMD	-	12-42	402	101	19595
6	M	7	DMD	-	45-50	198	99	9870
7	M	6	DMD	+	48-52	504	44	17500
8	M	3	DMD	-	no	104	455	7600
9	M	8	DMD	-	21-51	67	157	13200
10	M	5	DMD	-	8-11	124	202	10100
11	M	7	DMD	-	48-52	142	403	931
12	M	6	DMD	+	48-52	98	208	9680
13	M	8	DMD	-	45-50	206	189	5700
14	M	15 months	DMD	-	45	201	76	11400
15	M	18 months	DMD	-	45-50	186	48	14000

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CK: Creatine kinase; DMD: Duchenne muscular dystrophy; M: Male.

Statistical Analysis

Statistical evaluation of the data was performed using SPSS for Windows, Version 16.0 software (SPSS Inc., Chicago, IL, USA). Discrete variables (e.g., muscular biopsy findings, genetic analysis findings) were presented as number (n) and percentage (%) and continuous variables (e.g., age, height, body weight, echocardiography findings) were presented as mean±SD and with median and minimum-maximum values, as needed. Paired comparisons between corrected independent groups were performed using the Student's t-test or the Mann-Whitney U test. A value of $p < 0.05$ was considered statistically significant.

Discussion

DMD and its milder form, Becker muscular dystrophy (BMD), are X-linked recessive forms of muscular dystrophy caused by mutations in the dystrophin gene on chromosome Xp21.2.^[6, 7] The typical symptom of proximal muscle weakness often appears before the age of 5 years and cardiac involvement develops after muscular involvement.^[8] Consistent with the literature, in the current study, the mean age at the onset of DMD was 4.1 ± 2.4 years. It is commonly known that cardiac involvement occurs in 90% of DMD patients, depending on the stage of the disease, with subclinical cardiac involvement starting in the first decade, and cardiovascular symptoms appearing after the development of cardiomyopathy in the second decade. Preclinical cardiac involvement is present in 26% of patients aged less than 6 years, may be 62% in patients aged 6 to 10 years, and can be even greater in older children.^[8, 9] Cardiac involvement was present in 2 patients in this study. This low rate of cardiac involvement may be attributed to the fact that the other patients were relatively younger and had not had routine cardiac screening. DMD and BMD affect 1 in 3,500 children. Therefore, a prenatal genetic diagnosis is highly recommended for families with a DMD- or BMD-affected child. In isolated cases, the risk of the mother being a carrier is 2/3 (67%), so genetic counseling is crucial for those mothers considering another pregnancy. If pregnancy occurs, prenatal genetic testing is highly important for the fetus. Approximately one-third of isolated cases result from new mutations with no probability of carriership in the mother or other female relatives. DMD and BMD patients often present with gene deletions (60-65%) or duplications (10-15%). Currently, 2-layered multiplex PCR assay is the most widely used diagnostic method for the evaluation of exons where mutations are most frequently seen.^[10-12] In the current study patients, gene deletions were detected in 12 patients (80%) and duplications in 2 (13%), and 1 patient (7%) was diagnosed by biopsy. The deletions were

mostly detected between exons 45 and 52, which was consistent with the literature.^[10, 13, 14] Some other studies have shown that patients with deletions observed between exons 45 and 47 have become unable to walk without support after the age of 15 to 20 years.^[15] In the current study, the oldest child was 10 years old and 3 patients (20%) were unable to walk without support. The families of 3 patients had healthy babies after receiving genetic counseling. The provision of genetic counseling should be considered of the highest importance for the prevention of fatal disease, particularly in regions with a limited sociocultural context.

Conclusion

In conclusion, in a family with a DMD-affected child, carrier-ship should be investigated in all family members. Genetic counseling and prenatal genetic testing should be provided for these parents in order to avoid fatal disease in future pregnancies.

Disclosures

Ethics Committee Approval: Approval: Ethical approval was obtained from the Hospital Ethics Committee of Sütçü İmam University, Faculty of Medicine (Number: 195).

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