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Original Article

Duchenne muscular dystrophy patients diagnosed at the asymptomatic stage: What are the benefits of early diagnosis?

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ABSTRACT

Objectives: This study aimed to demonstrate whether a diagnosis given at the asymptomatic stage of patients with DMD can affect the clinical outcomes and to define the clinical characteristics of the patients.

Patients and methods: The cross-sectional study was conducted with 136 male patients (mean age: 8.8±3.7 years; range, 3 to 17 years) with DMD between March 2021 and February 2022. The patients were diagnosed through clinical presentation, pathology studies, and genetic testing. The demographic, clinical, and the laboratory data of the patients were recorded. The patients were evaluated in two groups: those diagnosed at the asymptomatic stage due to elevated creatine kinase (CK) and those diagnosed due to clinical symptoms. Patients were further stratified according to their age groups: those younger than 10 years and those aged 10 years or older. Hand grip, quadriceps muscle strength, and Vignos and Brooke motor functional assessment scales of the two groups were compared.

Results: In patients who were diagnosed with CK levels, CK elevation was significantly more common than other findings. When the age at diagnosis was evaluated, the age at diagnosis in those diagnosed with CK levels was statistically significantly lower than in those diagnosed with clinical findings. No significant difference was detected in clinical findings between the groups under the age of 10 years. Among patients aged 10 years or older, hand muscle strength, quadriceps muscle strength, and Vignos and Brooke motor function scale scores were significantly better in those diagnosed with CK levels compared to those diagnosed with clinical findings.

Conclusion: This study shows that early diagnosis in the preclinical period, which enables earlier medical treatment and rehabilitation, may have a positive effect on motor functions and the course of the disease.

Keywords: Diagnosis; Duchenne muscular dystrophy; rehabilitation.

Duchenne muscular dystrophy (DMD) is an X-linked, progressive muscle disease characterized by a dystrophin defect, affecting males in 1 in 5,000 live births. In the absence or deficiency of dystrophin, motor development is delayed due to progressive muscle damage. Difficulty in walking is the most important symptom due to the involvement of proximal muscles. Additionally, it presents with inability to run, difficulty climbing stairs, increased frequency of falls and falls, tiptoe walking, muscle pain, and cramps.

Typically diagnosed around the age of five years, the disease results in progressive muscle damage, with elevated creatine kinase (CK) levels, and muscle weakness. The addition of contractures and deformities to muscle weakness leads to functional disability. By 10 years of age, muscle weakness and functional impairment usually reach their peak. As the disease progresses, patients require a wheelchair between the ages of nine and 12. Progressive weakness in the upper extremity leads to impairment in daily living activities. Patients usually die due to cardiopulmonary complications in their third decade of life.[1,2]

Early and accurate diagnosis of DMD is important for both patients and caregivers. Early diagnosis enables families to make informed decisions about future care plans for the disease, facilitating the

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initiation of early therapy (e.g., steroids, rehabilitation, cardiac, orthopedic, and pulmonary management), which has been found to improve the quality of life and offer a longer life expectancy.[2]

Since early diagnosis is done at the asymptomatic stage, the incidental findings of biochemical test abnormalities, such as increases in transaminases and CK, can contribute to it. Weakness, clumsiness, Gowers' sign, difficulty climbing stairs, and tiptoe walking can be some of the findings. Increases in transaminases can lead to focusing on the hepatic causes, stalling the possible early diagnosis. Thus, using CK can be a safer and earlier way for the diagnostic process.

Creatine kinase is an enzyme that catalyzes the conversion of creatine and triphosphate to phosphocreatine and vice versa. It is found in the brain and muscles. Increasing in inflammation and muscle damage, CK can be increased in diseases involving the muscle, malignant hyperthermia, direct severe muscle damage, heart and central nervous system diseases, and peripheral artery diseases.[3,4] It is one of the most sensitive and reliable indicators of muscle damage and is related to the extent of damage and severity of the disease.[2] Creatine kinase elevation can occur in all conditions that cause muscle damage and is an important laboratory finding, particularly in dysferlinopathies.[4] It usually increases up to 10 times the upper limit within the first three years of life.[3]

The CK level is high from the neonatal period before clinical findings appear. As the disease progresses, CK levels decrease as muscle breakdown due to dystrophin deficiency increases. For CK levels, the European Academy of Neurology recommends further evaluation in patients whose CK levels are 1.5 times higher than the threshold value.[3,4] Early CK testing is emphasized in studies to prevent delayed diagnosis. It is also preferred due to its cost-effectiveness, high sensitivity, and specificity.[5]

This study aimed to describe the demographic, clinical, and laboratory characteristics of DMD patients and to evaluate the place and effect of biochemical markers impaired in the asymptomatic period in early diagnosis.

PATIENTS AND METHODS

This cross-sectional study was carried out at the Physical Medicine and Rehabilitation Clinic of İzmir Bakırçay University and İzmir Economics University Medicine Faculty and Neuromuscular Disease Center of Tepecik Training and Research Hospital, with 136 male patients (mean age: 8.8±3.7 years; range, 3 to 17 years), diagnosed with genetically and pathologically definitive DMD between March 2021 and February 2022. Demographic characteristics, age at diagnosis, type of diagnosis, symptoms, exercise status, medical treatments, Vignos and Brooke motor function scales, quadriceps and hand grip muscle strength, ankle joint range of motion measurements, and serum CK levels were recorded from the files of the patients. Ten years of age was considered the limit in muscle and functional changes (in terms of negative changes in the ability to get up from the ground, climb stairs, or stand) in boys with DMD in accordance with a previous study,[6] and the patients were stratified into two groups based on their ages. The first group consisted of those under the age of 10 years. The second group included those aged 10 years and over. The groups were further divided into two: those who were diagnosed with elevated CK without clinical symptoms at the first application and those who were diagnosed after applying to the health institution due to clinical symptoms (e.g., difficulty in walking, falling, fatigue, pain, weakness, cramps). The study protocol was approved by the İzmir Bakırçay University Ethics Committee (date: 19.01.2022, no: 28). A written informed consent was obtained from the parents and/or legal guardians of the patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Hand grip strength is considered an objective measurement in evaluating upper extremity performance. It is associated with upper extremity, whole body, and respiratory muscle strength. In the measurement, the muscle strength in the dominant hand was recorded as kg/force by taking the average of three repeated measurements made with a hand dynamometer (Baseline Push–Pull Dynamometer, Fabrication Enterprises, NY, USA).[7]

Brooke and Vignos scales were used to evaluate motor functions in DMD. The Vignos scale evaluates lower extremity motor function, and the Brooke scale evaluates upper extremity motor function. Increasing scores on both scales indicate deterioration of motor function.[8] The Vignos scale ranges from 1 to 10 points, while the Brooke scale ranges from 1 to 6 points (Appendix).

Statistical analysis

Data were analyzed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). All data were analyzed with descriptive statistics and were expressed as mean ± standard deviation (SD), median

(interquartile range) or frequency and percentage. The Shapiro-Wilk test was used to show whether the data conformed to normal distribution. Pearson's chi-square test and Fisher exact test were used to analyze categorical data. In intergroup comparisons of continuous data, parametric tests (independent sample t-test) were used for data that provided normal distribution, and nonparametric tests (Mann-Whitney U test) were used for data that did not provide normal distribution. A *p*-value <0.05 was considered statistically significant.

RESULTS

Eighty-four (61.8%) patients were under the age of 10 years, and 52 (38.2%) were over the age of 10 years. While the family history of 31 (22.1%) patients was positive, 105 (77.2%) were negative. The mean age at which patients first walked was 16.23±6.6 months (Table 1).

Initial reasons for admission were as follows: CK elevation (45.6%), walking difficulty (27.9%), other (16.2%), falls (2.9%), fatigue (2.2%), weakness (2.2%), pain (1.5%), and cramps (0.7%; Table 2).

Eighty-eight (64.7%) patients were in the ambulatory stage (Stage 1), 18 (13.2%) were in Stage 2, and 30 (22.1%) were in Stage 3. The treatment methods, use of orthoses, and exercise compliances are listed in Table 3.

In terms of diagnosis, the mean age at diagnosis of patients who were asymptomatic and diagnosed with elevated CK was 2.5±1.87 years. The mean age at diagnosis of clinically symptomatic patients were 4.0±2.38 years. The comparison of the age at diagnosis showed a significant difference between the groups (p<0.001).

No statistically significant difference was detected in clinical and laboratory parameters and motor function scales in patients under 10 years of age (p>0.05). Among patients aged 10 years or above, motor function scale scores and muscle strength of asymptomatic DMD patients with elevated CK at diagnosis were statistically significantly better compared to patients with symptoms at diagnosis (p<0.05; Table 5).

Among patients aged 10 years or above, clinical outcomes and motor function scale scores of patients with elevated CK at diagnosis were significantly better

TABLE 1
Demographic characteristics of patients with DMD

	n	%	Mean±SD
Age			
0-9 years old	84	61.8	
10-18 years old	52	38.2	
Family history			
Yes	31	22.8	
No	105	77.2	
Diagnosed in			
Tertiary care center/hospital	105	77.2	
Secondary level hospital	31	32.8	
Average walking time (months)			16.23±6.6
Medical treatment			
None	37	27.2	
Corticosteroid	25	18.4	
Corticosteroid + vitamin D	49	36.0	
Multiple medications	25	18.4	

SD: Standard deviation.

TABLE 2
Symptoms at first admission

	n	%
Fatigue	3	2.2
Fall	4	2.9
Walking difficulty	38	27.9
Weakness	3	2.2
Cramp	1	0.7
Pain	2	1.5
Other	23	16.9
Elevated creatine kinase	62	45.6
Total	136	100

TABLE 3
Use of orthoses and exercise

	n	%
Medical treatment		
None	37	27.2
Corticosteroid	25	18.4
Corticosteroid + Vitamin D	25	18.4
Multiple medications	49	36.0
Device usage		
None	43	31.6
AFO	64	47.1
Wheelchair	23	16.9
AFO + wheelchair	6	4.4
Exercise status		
Doing exercise regularly	134	98.4
not exercising	2	1.6

AFO: Ankle foot orthoses.

TABLE 4
Comparison in patients under 10 years of age

	Asymptomatic, diagnosed with elevated CK levels (n=34)					Symptomatic and diagnosed with clinical findings (n=31)					*p*
	n	%	Mean±SD	Median	25-75 percentile	n	%	Mean±SD	Median	25-75 percentile	
Ankle dorsiflexion			5.98±7.17	10	0-10			5.75±6.07	7.5	1.5-10	0.89
Vignos scale			1.82±1.26	2	1-2			2.19±1.51	2	1-2	0.28
Brooke scale			1.09±0.28	1	1-1			1.32±0.8	1	1-1	0.30
Creatine kinase (units/L)			14940±6728	16459	10104-20189			12482±5297	13959	8691-16836	0.18
Hand grip strength (kg)			3.57±2.54	3.5	2-5			4.32±2.00	3	4-6	0.25
Quadriceps muscle strength			4.45±0.67	5	4-5			4.37±0.79	5	4-5	0.42
Scoliosis	5	11.8				5	16.1				0.61

CK: Creatine kinase; SD: Standard deviation.

TABLE 5
Comparison in patients over 10 years of age

	Asymptomatic, diagnosed with elevated CK levels (n=28)					Symptomatic and diagnosed with clinical findings (n=43)					*p*
	n	%	Mean±SD	Median	25-75 percentile			Mean±SD	Median	25-75 percentile	
Ankle dorsiflexion			−6.71±14.6	0	−13.7-2.25			−14.1±15.2	−15	−22.5-0	0.46
Vignos scale			4.11±3.19	3	1-8			5.88±3.15	7	2-9	0.024*
Brooke scale			1.71±1.35	1	1-2			2.53±1.63	2	1-4	0.026*
Creatine kinase (units/L)			8811±10203	4413	2620-10868			4666±3807	3246	2180-6534	0.09
Hand grip strength (kg)			6.95±4.06	7.2	3.2-9.2			5.01±4.08	5	2-7	0.03*
Quadriceps muscle strength			3.42±1.23	3	3-4.25			2.58±1.38	2.5	1-4	0.021*
Scoliosis	14	50				26	60.5				0.38

CK: Creatine kinase; SD: Standard deviation; * p<0.05 is statistically significant (Mann-Whitney U test).

than those diagnosed with symptoms at diagnosis (p<0.05). The groups had no significant difference regarding mean ages (p>0.05).

DISCUSSION

The results of the study indicate that patients with DMD most often were diagnosed due to abnormal CK levels, followed by physical limitations such as walking abnormalities. Usually diagnosed in tertiary care centers, the ones who were diagnosed with higher CK levels had a mean age of 2.5±1.87 years at diagnosis. In contrast, the ones with the physical symptoms were diagnosed much later at a mean age of 4.0±2.38 years. While the comparison patients who were younger than 10 years did not show any significant differences in clinical characteristics regarding the method of diagnosis, the groups with patients aged 10 years and above showed that hand muscle strength, quadriceps muscle strength, and Vignos and Brooke motor function scale scores were better in the group diagnosed due to elevated CK levels.

Clinical and biochemical examinations performed in health institutions where patients are referred with different symptoms during childhood can guide the early diagnosis of pediatric neurologic diseases, which also include DMD. Blood CK levels are high in patients who are clinically asymptomatic in early childhood.[2] Although they may have been referred from different types of hospitals, most of the patients received their definitive diagnosis in the tertiary care hospitals, which is expected since the diagnostic methods such as genetic testing or muscle biopsies are usually performed in such centers.

Duchenne muscular dystrophy is a disease in which the muscle membrane is exposed to stress as a result of genetic mutations that prevent dystrophin production. Deficiency or absence of dystrophin leads to inadequate membrane stability, muscle breakdown, and increased CK levels. In the early period, motor disorders are subtle, and the emergence of these symptoms with the progression of the disease causes the diagnosis to be made around the ages of four to five years. Studies have shown that clinical symptoms appear later, leading to emphasis on elevated CK levels in early diagnosis.[9-12] The feasibility of screening for DMD in newborns was first demonstrated by the European Care Guideline for DMD (Treat-NMD) in the 1970s by measuring CK concentrations from dried blood samples; however, newborn screening studies for DMD in many countries were stopped, and the disease was not included in the screening panel, thus being limited to neonatal-onset disorders in which early treatment improves.[13,14] The emergence of new treatments has increased the interest in screening in the neonatal period by bringing CK testing before the onset of symptoms back to the agenda. Timonen et al.[14] performed screening for the CK-MM isoform in newborns and reported that CK levels made a good distinction between normal, unaffected, and DMD-affected populations, indicating suitability for DMD newborn screening. Consistent with our study, Weber et al.[15] evaluated 11 studies with 1,416,123 newborn samples. They reported that CK levels showed good accuracy in screening for cases of DMD, presenting a useful alternative to genetic testing in the early diagnosis of the disease. The patients diagnosed through elevated CK levels were younger at the time of diagnosis compared to those who were diagnosed through clinical symptoms. This finding fortifies the view that claims that patients with DMD can be diagnosed earlier when investigated through biochemical abnormalities, such as increased CK levels.

Even without considering the novel therapies that have the potential to alleviate the disease immensely, early diagnosis is of great importance for DMD patients. In the treatment of DMD, early initiation of the multidisciplinary care process with a patient-centered approach, regular monitoring, and treatments improve the quality of life and prolong life.[2]

Studies on new medical treatments for DMD have progressed rapidly in recent years. Both current and possible future treatments appear to rely on the initiation of treatment in the early stages, in which muscle breakdown and resulting complications such as joint deformities are not present, to achieve the best results. Currently, corticosteroids and physical therapy are the main treatment methods in DMD. Corticosteroids provide membrane stabilization. Starting steroid treatment at the appropriate time and continuing the treatment increases muscle strength and function. It is associated with prolonged ambulation time and has a positive effect on motor functions. While it has beneficial effects on scoliosis, pulmonary functions, and cardiac functions, studies also report an increased risk of fracture as a downside.[16,17]

Management of DMD includes multidisciplinary treatment and is also known to affect disease progression. Therefore, early diagnosis is crucial for appropriate treatment and monitoring of possible complications.[18] It is well-documented that the disease progresses with increasing age. Humbertclaude et al.[18] reported that the decrease in motor and respiratory functions was evident under the age of 10 years, and the deterioration in cardiac functions was evident above the age of 10 years. The results of our study also showed that the patients had a great adherence to regular exercise therapy (98%) designed for them. Exercise is known to have positive effects on muscle strength, endurance, and respiratory muscle strength, and exercise programs reduce the risk of developing complications when started early.[16,17] Thus, it can be stated that the significant difference in motor function scale scores and hand grip strength, particularly in the late period, may have been partly due to the initiation time of the exercise program.

No statistically significant difference was detected in clinical and laboratory findings under the age of 10 years in those who were asymptomatic and diagnosed with elevated CK and those diagnosed with symptomatic findings. This lack of difference was possibly due to the clinical progression being mild in this stage, lacking demonstrable difference. Although prospective future studies may show a possible difference in the younger group, it is worthy of discussion whether this difference would be clinically significant.

Hand muscle strength, quadriceps muscle strength, and Vignos and Brooke motor function scale score were found to be statistically significantly higher in patients over the age of 10 years diagnosed with elevated CK. Diagnosis at an early age allows medical, rehabilitative and care strategies to begin

early. Steroid treatment is still the basis of the care strategy in DMD. Henricson et al.[19] evaluated 340 DMD patients receiving steroid treatment and reported that loss of strength decreased and functional abilities were preserved in patients who started treatment under the age of 10 and continued treatment. Early initiation of steroid treatment has been reported to have positive effects on the progression of the disease, particularly on muscle strength, respiration, scoliosis, and cardiac functions.[19] Early initiation of pharmacological therapy and physical therapy in DMD patients has also resulted in prolonged ambulation and reduced significant complications such as contracture, deformity, and scoliosis, with patients being able to function better in all areas of life.[20]

Although DMD symptoms can develop early, the condition is frequently diagnosed at four years of age or later, and it can take up to two years to find the cause of symptoms. Avoiding diagnostic delays becomes more crucial when disease-modifying medications for DMD become accessible. These treatments should preferably be started early to prevent irreparable muscle degeneration from occurring. The earliest possible diagnosis of DMD reduces the risk of the disease and facilitates timely genetic counseling, carrier status assessment, initiation of multidisciplinary standard care, initiation of appropriate treatments at the right time, and characterization of the genetic mutations to precisely determine suitability for access to drugs targeting specific mutations.[21] The results of our study underline the importance of early diagnosis obtained through elevated CK levels, which can have effects on the prognosis of the disease as well.

Several limitations could be noted in this study. The main limitation is the cross-sectional nature of the study. A design that included longitudinal follow-ups, either a cohort or an interventional study, could give better evidence on the issues that were hypothesized. While the total number of participants is not very small, and DMD is a relatively rare disease, a large number of participants could give clearer results, especially in the subgroup analyses.

In conclusion, most current therapies are beneficial, as long as the patients have sufficient muscle tissue to be protected, which corresponds to the earlier stages of the disease. Thus, researchers and clinicians should promote the methods for earlier diagnosis, which includes biochemical tests, genetic screening, or, in the worst case, early identification through subtle clinical signs. Since CK levels is one of these methods, early screening of CK levels is encouraged. Further studies investigating the usefulness of diagnostic methods for the prognosis of the disease are needed.

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

Author Contributions: Idea, literatüre review, writing, references, critical review: F.M.S., G.T.; Design: F.M.S., G.T., F.B., M.Y.K.; Control: M.Y.K.; Analysis: G.T.; Materials: All authors.

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APPENDIX

Vignos scale

1. Walks and climbs steps without assistance
2. Walks and climbs the steps holding on to the banisters
3. Climbs the steps slowly holding on to the banisters.
4. Walks unaided and gets up from a chair but cannot climb steps.
5. Walks unaided but cannot get up from chair or walk up steps.
6. Can walk only with assistance or with a walking device.
7. Walks with a walking device but needs help with balance
8. Stands with a walking device but cannot walk even with assistance.
9. Is in a wheelchair.
10. Is bedridden.

Brooke scale

1. Standing with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head.
2. The patient can raise the arms above the head only by flexing the elbow or by using accessory muscles (i.e. by shortening the circumference of the movement)
3. The patient cannot raise hands above the head but can raise an 8-oz. glass of water to the mouth (using both hands if necessary).
4. The patient can raise hands to mouth but cannot raise 8-oz. glass of water to the mouth
5. The patient cannot raise hands to the mouth but can use the hands to hold a pen or to pick up pennies from a table.
6. The patient cannot raise hands to the mouth and has no useful function of the hands.