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Clinical-evolutionary considerations in Duchenne Dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a severe, progressive and incurable X-linked genetic disorder. The article presents 18 children with DMD admitted between 2016-2022 in the Pediatric Clinic II, Emergency County Hospital in Craiova. The study looked at: the distribution according to residence, the average age when they walked, when they were diagnosed and when they walked in a wheelchair, heredocollateral and pathological antecedents, clinical manifestations, nutritional status, genetic tests and the evolution of these patients.

Keywords: Duchenne muscular dystrophy, boys, childhood disability

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common inherited X-linked muscle disease and shows no predilection for race or ethnic group [1]. It is a progressive, incurable disease [2]. DMD affects boys; 1 in 3500-5000 newborn boys suffers from this condition [3]. DMD patients lack the functional dystrophin protein caused by more than 7000 mutations in the dystrophin gene, which is one of the largest human genes with 79 exons and 2.5Mb of DNA [2,4,5].

Interestingly, in healthy skeletal muscle dystrophin is 427 kD and represents only 0.002% of total striated muscle protein, but its absence leads to severe deleterious effects on muscle functionality [6,7].

About 2/3 of cases are maternally inherited, 1/3 occur as a result of spontaneous mutations [8]. DMD is caused by mutations in the DMD gene, leading to progressive muscle weakness that eventually leads to loss of independent ambulation in early adolescence, scoliosis, cardiomyopathies, respiratory failure, and death before the 3rd or 4th decade of life, due to cardio-respiratory complications [9]. DMD is now recognized as a multisystemic and progressive disease [10].

In this study we aimed an analysis of DMD cases admitted into our clinic from the point of view of age at the time of diagnosis, age at the time of admission into our clinic, pathological antecedents, clinical manifestations in early childhood and adolescence, manifestations of cardiac events and their incidence, respiratory manifestations and their frequency, average values of serum creatine kinase, genetic tests, nutritional status and evolution of these patients.

MATERIAL AND METHOD

The study took place in the Pediatric Clinic II, Emergency County Hospital in Craiova, in male chil-

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dren diagnosed with progressive muscular dystrophy, hospitalized during 01.01.2016-31.12.2022.

In the group of children, the following were performed: medical history, objective examination, creatine kinase and creatine kinase-MB dosage by spectrophotometry method (Architect C8000 device), cardiological examination and cardiac ultrasound (GE Vivid E95 Ultrasound device), spirometry (Spirodoc Myr device) and genetic tests by the MLPA (multiplex ligation-dependent probe amplification) technique.

The children with DMD hospitalized in the Pediatric Clinic come from several areas of the country and from Chisinau, thanks to the existence of the Association Parent Project Romania - Association for research and assistance in DMD based in Craiova, and thanks to the Regional Center for Medical Genetics Craiova. During hospitalization, children with DMD were taken care of by a multidisciplinary team: pediatrician, geneticist, pulmonologist, cardiologist, pediatric surgeon.

Parents gave their written consent for the participation in the study.

RESULTS

During this period, 18 male children were hospitalized with the diagnosis of progressive muscular dystrophy.

The background of DMD patients was urban in 11 (61%) and rural in 7 (39%) (Figure 1).

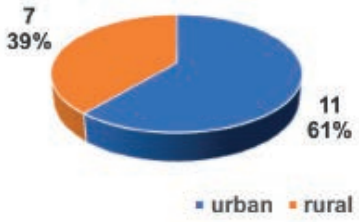

FIGURE 1. The background of children with DMD

The counties where DMD patients come from are: Dolj 5, Gorj 2, 1 patient each from Olt, Mehedinti, Caras-Severin, Galati, Braila, Covasna, Vaslui, Buzau, Maramures, Bucharest and Chisinev (Figure 2).

FIGURE 2. Distribution of DMD patients according to the counties they come from

The hereditary-collateral antecedents in children with DMD showed: 4 children with 1 healthy sister each, 2 children with 1 healthy brother each, 1 of the patients has an uncle from the mother's side who had the same manifestations of the disease, but was not diagnosed and died at a young age, and 4 genetically tested mothers have the same result as their children.

The average age at which children with DMD walked was 17.4 months ± 1.62, with ranges between 15–20 months.

The average age at diagnosis was 5 years 6 months ± 2 years and 7 months, with a range of 1-12 years. There are children who were diagnosed at a young age, but there are also children diagnosed late at the age of 12.

The age at which they were admitted into our clinic: 12 years ±4.5 (range 2-17 years).

The pathological antecedents found in patients with DMD were: pulmonary tuberculosis in 2 patients, HBP in 3 children, Ross operation for severe aortic stenosis post- bacterial endocarditis, inferior lateral myocardial infarction, adenoidectomy, autism and pityriasis versicolor in 1 child each (Table 1).

TABLE 1. Pathological history present in patients with DMD

pathological history	No. of cases
pulmonary tuberculosis	**2**
HBP	**3**
Ross operation for sever aortic stenosis post-bacterial endocarditis	**1**
inferior lateral myocardial infarction	**1**
adenoidectomy	**1**
autism	**1**
pityriasis versicolor	**1**

We analyzed clinical manifestations in patients with DMD, divided into 2 groups: under 12 years of age and children over 12 years of age, because clinical manifestations differ according to age (Table 2).

In children with DMD under 12 years of age, we observed the presence of the following clinical manifestations: full moon facies in 3 children, hyperlordosis in 3, hypertrophy of the ankles in 4 children, wide-based waddling in 3 children, muscle fatigue at low effort in 3 children, difficulty climbing stairs and running in 3 children, in 2 eight year old children who had not received previous treatment, they were immobilized in wheelchairs with severe motor impairments with flexed legs, manifestations that occur in older children.

In children over 12 years of age, the clinical manifestations were: wheelchair dependence in 12 children, hypercorticism in 9 children, deformed thorax/congested sternum (pectus excavatum) in 11 children, generalized muscle atrophy, generalized muscle hypotonia in 5 children, lack of muscle strength including fingers in 6 children, foot malpo-

TABLE 2. Clinical manifestations in children with DMD

Clinical manifestations in children under 12 years of age (N= 7)		Clinical manifestations in children over 12 years of age (N= 11)	
moonlike facies	3	wheelchair dependence	12
hyperlordosis	3	hypercorticism	9
hypertrophy of the calf muscles	4	deformed thorax/ pectus excavatum	11
waddle with wide base	3	generalized muscle aprophy	5
muscle fatigue at low effort	3	generalized muscle hypotonia	5
difficulty in climbing stairs and running	3	lack of muscular force, in fingers too	6
severe motor deficitis, legs in flexion	2 no prior therapy	malpositioning of feet	4
		talo-crural tendon retractions	4
		thoracolumbar kyphoscoliosis	4
		limited extension of elbows, knees	5
		hyperlordosis	5
		constipation	11
		osteoporosis	6
		low intellect	3
		emotional disturbance with depressive notes	1
		sleep apnea syndrome	1
		dizziness when changing position	1

sition and talo-crural tendon retraction, thoracolumbar kyphoscoliosis in 4 children, limitation of elbow and knee extension, hyperlordosis in 5 children, constipation in 11 children, osteoporosis in 6 children, reduced intellect in 3 children, emotional disorder with depressive notes, sleep apnea syndrome, dizziness when changing position in 1 child with DMD.

Nutritional status in children with DMD: 4 patients with normal weight (22.2%), 10 with obesity (55.6%) and 4 with cachexia (22.2%).

Cardiac manifestations in children with DMD were found in 16 (88.9%): NYHA class III heart failure with low ejection fraction in 2 children, dilated cardiomyopathy with moderate systolic dysfunction in 3 children, severe systolic dysfunction in 2 children, cardiomyopathy secondary to Duchenne disease in 5 children, hypertension in 3 children, mitral insufficiency and hypokinesia at the apex in 2 children each, aortic insufficiency and mitral valve prolapse in 1 child each (Table 3).

TABLE 3. Cardiac manifestations in children with DMD

Cardiac manifestations	No. of cases
NYHA class III heart failure with low ejection fraction	2
dilated cardiomyopathy with moderate systolic dysfunction	3
severe systolic dysfunction	2
cardiomyopathy secondary to Duchenne disease	5
hypertension	3
mitral insufficiency	2
hypokinesia at the apex	2
aortic insufficiency	1
mitral valve prolapse	1

Pulmonary manifestations were present in 15 children with DMD (83.3%), 6 children had moderate ventilatory dysfunction, and 9 had severe ventilatory dysfunction.

Genetic testing was performed on all patients with DMD, but not all patients brought genetic testing results to admission. Of the 18 children with DMD in the study, only 12 had genetic test results (Table 4).

TABLE 4. Genetic tests in children with DMD

Genetic tests	No. of children
Mutation of exon 44 in the dystrophin gene	1
Deletion of exons 3-13 in the dystrophin gene	1
Hemizygous duplication of exon 2 in the dystrophin gene	1
Deletion of exons 46-47 in the dystrophin gene	1
Hemizygous deletion of exons 45,46,47 and 48 in the dystrophin gene	1
Deletion of exon 44 in the dystrophin gene	1
Hemizygous deletion of exons 35,36,37,38,39,40, 41,42,43,44,45 in the dystrophin gene	1
Deletion of exons 48-50 in the dystrophin gene	1
C5697del Mutation	1
Hemizygous deletion of exon 45 in the dystrophin gene	1
Deletion of exon 46-50	1

Serum creatine kinase values in hospitalized DMD children were: 2563.793 ±2360.88 IU/L, with limits 1301.57-10359 IU/L. creatine kinase isoenzyme MB had the average value in hospitalized patients with DMD of 87.206±60.158 IU/L, with limits 26.74-302 IU/L (Table 5).

Of the 18 children with DMD in the study, 5 (28%) over the age of 18 died in the period 2020-2021 (Figure 3).

TABLE 5. Creatine kinase and creatine kinase isoenzyme MB in children with DMD

	Average value	Standard Deviation	Limits
Creatine kinase	2563.793 IU/L	±2360.88	1301.57-10359 IU/L
Creatine kinase isoenzyme MB	87.206 IU/L	±60.158	26.74-302 IU/L

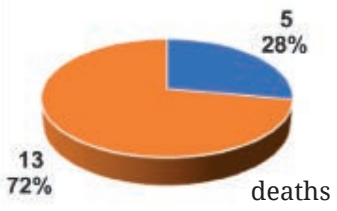

FIGURE 3. DMD children evolution

DISCUSSIONS

First described in 1868 by Guillaume Duchenne de Boulogne, DMD is a rare disease. Affected patients are male, while females are likely to be asymptomatic healthy carriers.

Of the 18 patients with DMD in the study, 61% came from the urban environment, and 39% from the countryside.

The average age at which they walked was delayed: 17.4±1.62 months, with limits between 15–20 months, as described in the literature [9,11]. The average age at diagnosis was 5 years 6 months ± 2 years and 7 months, with a range of 1-12 years. There are children who were diagnosed at a young age, but there are also children diagnosed late at the age of 12.

Although the disease is present from birth, clinical manifestations become apparent between 3-5 years of age [12,13]. The clinical manifestations presented by DMD patients in our study are also described in the literature [14,15]. Related to scoliosis, 60% of children with DMD have scoliosis by age 15 [14]. The children over 12 years old, all were dependent on a wheelchair and a permanent companion, all had osteoporosis. 8 out of 11 children with DMD showed autism, reduced intellect, emotional disturbances with depressive notes, as we found described in other articles, because dystrophin is also expressed in neural tissues [13,15,16].

Cardiac manifestations were present in 88.9% of DMD patients. The most frequent cardiac manifestations were: NYHA class II heart failure with low ejection fraction, dilated cardiomyopathy with moderate systolic dysfunction, severe systolic dysfunction, cardiomyopathy secondary to Duchenne disease, HBP, manifestations also described by other authors [17,18,19].

Corticosteroid treatment has been associated with delayed onset of cardiomyopathy [20,21]. 68% to 93% of children with DMD have been diagnosed with cardiomyopathy by the age of 20 [22].

Respiratory manifestations were present in 83.4% of patients: 6 with mild to moderate respiratory dysfunction and 9 with severe respiratory dysfunction. Ventilatory failure due to progressive loss of respiratory muscles is the main cause of death in DMD [19]. Respiratory involvement occurs in approximately half of adolescent DMD patients, and estimates suggest that 40–50% of DMD patients would require ventilatory support after the age of 20 [23].

Approximately 95% of DMD patients become wheelchair bound by the age of 15 [24].

In a study conducted in 2023, it is mentioned that neurodepressive, emotional and behavioral symptoms have a higher prevalence in genotypes affecting the 3 end of the dystrophin gene. Neurological involvement is seen in approximately half of DMD patients [25].

Genetic tests were performed on all patients, but not all hospitalized children had genetic test results on admission. Of the 18 patients with DMD, 12 had the results of genetic tests, they showed deletions, mutations, duplications.

Creatine kinase had an average value of 2563.793±2360.98 IU/L, with limits between 1301.57±10359 IU/L. Serum creatine kinase measurements are elevated before the onset of clinical signs and may also be elevated in the newborn. The level peaks at the age of 20 and can be more than 10-20 times the upper limit of normal [1].

Of the 18 patients in the study, 28% died over the age of 18, in the period 2020-2021.

CONCLUSIONS

The average age at diagnosis was 5 years 6 months ±2 years 7 months (with limits 1-12 years).

88.9% of patients had cardiac manifestations and 83.3% had pulmonary manifestations.

28% of patients died over the age of 18.

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REFERENCES

1. Venugopal V, Plavakis S, Duchenne Muscular Dystrophy tatPearls Publishing; 2022 Jan (Pubmed).
2. Loboda A, Dulak J. Muscle and cardiac therapeutic strategies for Duchenne muscular dystrophy: past, present, and future. *Pharmacol Rep.* 2020 Oct;72(5):1227-1263 (Pubmed).
3. Kairullin AE, Grishin SN, Ziganshin AV. P2 Receptor Signaling in Motor Units in Muscular Dystrophy, *Int. J. Mol. Sci.* 2023, 24(2), 1587.
4. Carter JE, Sheehan DW, Prochorof A, Birnkrant DJ. Muscular Dystrophies. *Clin Chest Med.* 2018 Jun;39(2):377-389.
5. Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Hum Mutat.* 2015 Apr;36(4):395-402.
6. Erkut E, Yokota T. CRISPR Therapeutics for Duchenne Muscular Dystrophy. *Int J Mol Sci.* 2022 Feb 6;23(3):1832.
7. Hoffman EP, Brown RH. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell.* 1987 Dec 24;51(6):919-28.
8. Rus AA, Deutekon JCT, Fokkema IF. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve.* 2006 Aug;34(2):135-44.
9. Mah JK. Current and emerging treatment strategies for Duchenne muscular dystrophy. Neuropsychiatr Dis Treat. 2016; 12: 1795–1807.
10. Suthar R, Sankhyan N. Duchenne Muscular Dystrophy: A Practice Update. *Indian J Pediatr.* 2018 Apr;85(4):276-281.
11. https://www.poliana.ro, viata cu distrofia musculara
12. Twee TD. Muscular Dystrophy Clinical Presentation. Jan 24, 2023;Pubmed
13. Plesca Doina. Afectiunile neuromusculare in copilarie. Bucuresti: Ed. Didactică și pedagogică, 1999.
14. Duan D, Goemans N, Takeda S. Duchenne muscular dystrophy. *Nat Rev Dis Primers.* 2021 Feb 18;7(1):13.
15. Tsuda T. Clinical Manifestations and Overall Management Strategies for Duchenne Muscular Dystrophy. *Methods Mol Biol.* 2018;1687:19-28.
16. Saito Y, Takeshita E, Komaki H Determining neurodevelopmental manifestations in Duchenne muscular dystrophy using a battery of brief tests. *J Neurol Sci.* 2022 Sep 15;440:120340.
17. Fayssoil A, Abasse S, Silverston K. Cardiac Involvement Classification and Therapeutic Management in Patients with Duchenne Muscular Dystrophy. *J Neuromuscul Dis.* 2017;4(1):17-23.
18. Mavrogeni S, Mavrogeni G, Papavasiliuou A. Cardiac Involvement in Duchenne Muscular Dystrophy and Related Dystrophinopathies, *Methods Mol Biol.* 2018;1687:31-42.
19. Pennati F, LoMauro A, D'Angelo F. Non-Invasive Respiratory Assessment in Duchenne Muscular Dystrophy: From Clinical Research to Outcome Measures. *Life* (Basel). 2021 Sep 10;11(9):947.
20. Barber B, Andrews J, Lu Z. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. *J Pediatr.* 2013 Oct;163(4):1080-4.e1.
21. Bourke J, Turner C, Bradlow B. Cardiac care of children with dystrophinopathy and females carrying DMD-gene variations. *Open Heart.* 2022;9:e00197.
22. Kim S, Zhu Y, Romitti P. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. *Neuromuscul Disord.* 2017 Aug; 27(8): 730–737.
23. McDonald CM, Henricson EK. Abresch RTet al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet.* 2017 Nov 22. pii: S0140-6736(17)32160-8.
24. Szabo S, Klimchak A, Qian C. Characterizing the Occurrence of Key Clinical Milestones in Duchenne Muscular Dystrophy in the United States Using Real-World Data. *J Neuromuscul Dis.* 2022;9(6):689-699.
25. Maresh K, Papageorgiou A, Ridout D. Startle responses in Duchenne muscular dystrophy: a novel biomarker of brain dystrophin deficiency, *Brain.* 2023;146(1):252–65