WELIAN-POLUS, Iwona, MAZUR, Bartosz, BIELAK, Michał, MAZUR, Magdalena, RYPULAK, Elżbieta, WILANOWSKA, Wiktoria, GREGUŁA, Anna, STACHYRAK, Karol, MIKA, Dawid and TUREK, Kamila. Aggravation of Cardiovascular and Respiratory Decline in Advanced Duchenne Muscular Dystrophy Complicated by Dilated Cardiomyopathy – Case Study and Review of Literature. Journal of Education, Health and Sport. 2024;68:50187. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.68.50187
https://apcz.umk.pl/JEHS/article/view/50187

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 14.04.2024. Revised: 05.05.2024. Accepted: 08.05.2024. Published: 14.05.2024.

Aggravation of Cardiovascular and Respiratory Decline in Advanced Duchenne Muscular Dystrophy Complicated by Dilated Cardiomyopathy – Case Study and Review of Literature

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Abstract

Introduction:
Duchenne muscular dystrophy is a genetic X-linked recessive disorder. This condition is characterized by progressive loss of muscle tissue. Thus, it results in deterioration and inability to perform basic motor skills such as independent movement or breathing. Due to progressive muscle weakness, patients with advanced stages of DMD require mechanical ventilation, feeding, and rehabilitation. Furthermore, alterations in cardiac muscle lead to cardiomyopathy. Despite advanced supportive treatment, DMD is a fatal disease.

Purpose:

The aim of the paper is to present, using a case study description, the current standards of treatment for patients with Duchenne muscular dystrophy as well as the current state of knowledge and new discoveries regarding this medical condition.

Material and methods
The patient's medical records were analyzed and available literature in PubMed was reviewed to write this article using the keywords: „Duchenne muscular dystrophy”; „cardiomyopathy”; „mechanical ventilation”; „gene therapy”;

Conclusions

Early detection of respiratory and circulatory insufficiency improves the patient's quality of life. Many patients with an advanced stage of Duchenne muscular dystrophy need specialized treatment, for example, in the intensive care unit. Therefore there is an urgent need for new treatment methods, such as gene therapies, which can slow down or break the course of the disease. New discoveries and the implementation of new treatment standards can enhance the quality of life for patients and extend their lifespans.

Keywords: Duchenne muscular dystrophy; cardiomyopathy; mechanical ventilation; gene therapy;

Introduction

Duchenne muscular dystrophy (DMD) is a genetic X-linked recessive disorder. DMD is the most common genetically determined dystrophinopathy. The incidence of this condition ranges from 1 in 3500 to 1 in 5000 live male births [1,2,3,4]. DMD is caused by mutation in the gene encoding dystrophin, a protein found in the muscle cell membrane (sarcolemma). The lack of dystrophin results in the disintegration of sarcolemma in both skeletal and cardiac muscles. This is the cause of progressive limb weakness, which leads to the loss of ambulation typically in the second decade of life [2]. As a result of respiratory muscle impairment patients get hypoventilation and subsequent restrictive respiratory failure. Due to obstructive sleep apnea (OSA) treatment initially starts at home with night mechanical ventilation. In subsequent stages likewise 24 hour ventilation [5, 6, 7]. Approximately 25% of patients with DMD below the age of 6 develop cardiomyopathy, although the first symptoms of cardiac dysfunction appear in the second decade of life. Cardiomyopathy is recognised in almost all patients above the age of 18. Cardiac complications present as dilated

cardiomyopathy and arrhythmias [5, 8]. Once respiratory failure was the most common cause of death in patients with DMD. However, with the spread use of home mechanical ventilation, the average lifespan has extended to more than 20 years [9]. Thus, currently cardiomyopathy has become the leading cause of death in patients with DMD [10].

Material and methods

The patient's medical records were analyzed and available literature in PubMed was reviewed to write this article using the keywords: „Duchenne muscular dystrophy”; „cardiomyopathy”; „mechanical ventilation”; „gene therapy”;

Case report

A 28-year-old male diagnosed with DMD was admitted to the Intensive Care Unit (ICU) due to respiratory and circulatory failure exacerbation. He has been mechanically ventilated at home through a tracheostomy tube for 12 years. The patient suffered from congestive heart failure and obesity (BMI 60).

Chest X-ray revealed a small amount of pleural effusion and an enlarged cardiac silhouette. Echocardiography confirmed impaired contractility and enlargement of the heart. Despite extreme obesity, the patient was malnourished. Both protein (5.1 g/dL) and albumin (2.8 g/dL) concentration were low. Thus, intensive gastric feeding with enteral nutrition was implemented.

Hypotension was treated with norepinephrine infusion. Hypovolemia was recognised and additional intravenous fluid therapy was implemented. The patient was treated with a beta-blocker and a thiazide diuretic because of heart failure.

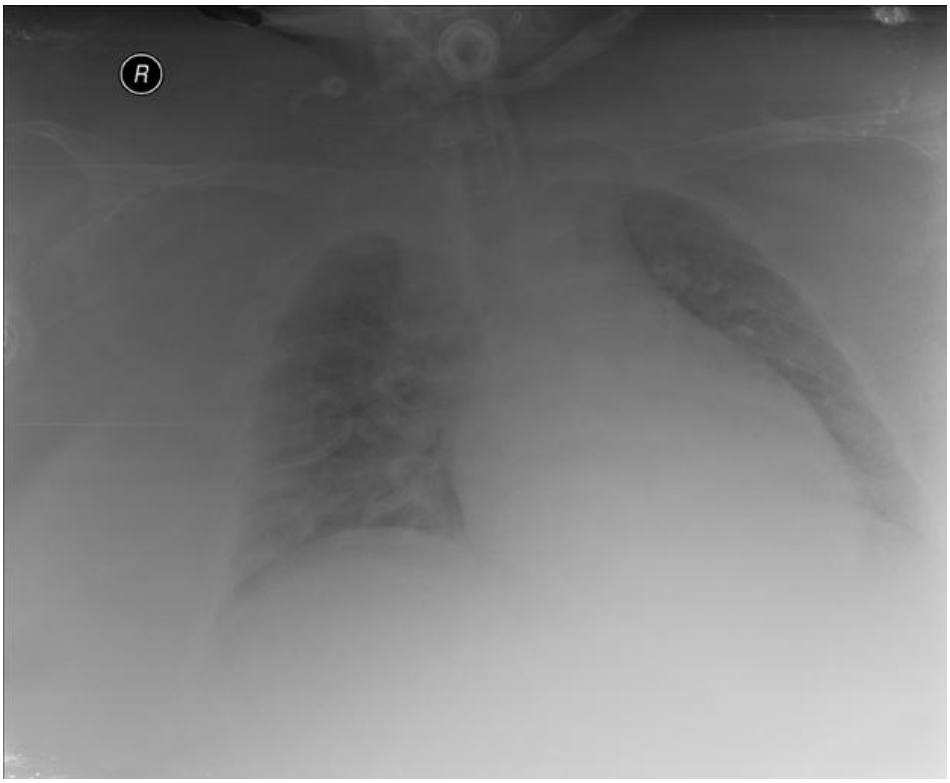

Figure 1. Lung X-ray after pleural drainage

Urinary tract infection was suspected because of elevated inflammatory markers (CRP>200 mg/L, WBC>20 K/uL) and an indwelling urinary catheter. Urinalysis showed cloudy urine with leukocyturia. Aerobic urine culture was negative. Fosfomycin was applied, and the bladder was rinsed with citrate and polihexanide. Other sources of the inflammatory process were excluded. The patient required thromboprophylaxis with apixaban in the prevention of thrombosis.

Unfortunately, only a slight improvement in his condition was observed in the following days. Because of the progressive nature of DMD and no prognosis for a real improvement, the patient was discharged from the hospital On the fifth day of the ICU stay in moderate condition. The decision was consulted with the patient's family and with the patient himself.

Discussion and conclusions

The above-described patient struggled with several complications of DMD, such as respiratory failure, cardiomyopathy and circulatory failure, extreme obesity and exacerbating cystitis. All of the above caused deterioration in the patien's condition. This resulted in the need of treatment in the ICU [8]. Imaging studies revealed an enlarged heart silhouette and decreased left ventricular contractility, indicative of cardiomyopathy.

Cardiomyopathy is currently one of the leading causes of death in patients with DMD. The incidence of cardiomyopathy increases with age. It develops due to the absence of the dystrophin protein, which stabilizes the cell's cytoplasmic membrane by transferring the forces generated by sarcomere contraction to the extracellular space. Dystrophin deficiency causes increased calcium influx into the muscle cells, resulting in death. Progressive cardiac fibrosis and increasing left ventricular failure lead to cardiomyopathy over time [9, 10]. Typical signs of heart failure include effort dyspnea or effort intolerance. It is determined by the lack of physical activity in patients due to the weakening of muscle strength. Symptoms such as fatigue or effort intolerance are attributed to the degradation of muscle mass [11]. Common ECG findings include right bundle branch block, nodal tachycardia and right axis deviation. Echocardiography shows dilatation of the left ventricle and its systolic dysfunction (left ventricule ejection fraction- LVEF <55%) [10]. From the age of 10, the patient should be carefully observed for abnormalities in the functioning of the heart by performing tests such as echocardiography and ECG once every two years [11].

Corticosteroids are the first-line medication in the treatment of DMD-related cardiomyopathy. They reduce inflammation, slow disease progression, and inhibit heart fibrosis [10].

Beta-blockers and ACE inhibitors are used in heart failure induced by cardiomyopathies during Duchenne's disease. Angiotensin-converting enzyme (ACE) inhibitors are currently recommended as a first-line drug for treating cardiomyopathy in DMD. They reduce aldosterone secretion and inhibit the formation of angiotensin II. This causes vasodilation, a decrease in peripheral resistance, and a decrease in cardiac output, reducing left ventricular hypertrophy [10, 11]. Beta-blockers inhibit the activity of the sympathetic nervous system. They have a negative inotropic and chronotropic effect on the heart and reduce arterial pressure [11, 12]. A cohort study on the prophylactic administration of ACE inhibitors in asymptomatic adolescents with DMD is currently being conducted. The data shows that

prophylactic therapy with ACE inhibitors significantly reduces the risk of death and the number of hospitalizations [12].

Malnutrition is widespread among critically-ill patients and affects up to 50% of them [13]. Screening patients with standard questionnaires, such as the Nutritional Risk Score (NRS) 2002, may help to identify malnourished individuals. However, some laboratory tests could be used when a medical interview is difficult to obtain [14]. Most ICU patients could require high-protein nutrition [15].

As DMD is progressive loss of muscle tissue, mechanical ventilation enables oxygenation in respiratory muscles weakness and restrictive breathing disorders. Most patients are mechanically ventilated at home through a tracheostomy tube [16, 17]. Prolonged mechanical ventilation may cause insomnia, pain, daytime sleepiness and digestive problems, yet patients do not complain about their quality of life [18]. Studies by Fayssoil et al. found that in patients with DMD undergoing mechanical ventilation, accurate ventilator setting reduces the afterload of the left ventricle (LV). This improves LV function and also reduces pulmonary systolic pressure due to reduced pulmonary resistance [6, 19].

Despithe increasingly advanced therapies DMD is a fatal disease. Thus, essential part of the treatment is to inform patient and the patient's family about end-of-life care. The SPIKES protocol may be used to pass on unfortunate information [20].

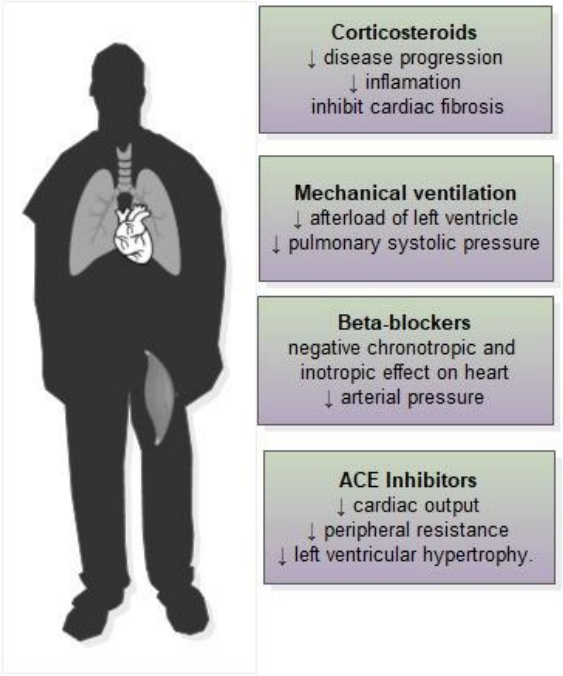

Figure 2. Drug effects in Duchenne muscular atrophy [20]

In recent years, novel therapies have emerged new therapeutic options and limit the progression of DMD. These include stem-cell and gene therapies targeted at restoring the function of the damaged dystrophin protein [5]. One of the strategies of gene therapy in DMD is exon-skipping therapy. It aims to bypass the mutated exons in the gene of the damaged protein. The medications include eteplirsen and golodirsen and viltolarsen which excludes exon 51 and bypass exon 53, respectively [21]. Camisersen is a phosphorodiamidate morpholino oligomer that allows for correction of the reading frame of a mutant pre-mRNA fragment of dystrophin gene transcript and produces a truncated but properly functioning dystrophin protein [22, 23]. Camisersen has already been approved for use in patients In clinical trials. This medication has been shown to increase the amount of dystrophin in the muscles of patients with DMD gene mutations amenable to exon 45 skipping. It is estimated that approximately 8% of cases of patients with DMD may benefit from this treatment [24]. Another promising therapy for patients with DMD is ataluren. It increases the amount of dystrophin in patients with a nonsense mutation in the dystrophin gene, who account for approximately 10-15% of DMD patients [25]. In the phase III STRIDE clinical trials, it has been shown that ataluren delays the progression of the disease by about 2 years and

significantly improves the distance covered during the 6-minute walk distance test [26, 27]. Other phase III drugs are PF-06939926 and Delandistrogene Moxeparvovec. Their mechanism of action is to introduce a correct copy of the dystrophin-encoding gene into a muscle cell with an adenovirus vector [28, 29, 30, 31].

DMD is a progressive disease with multiple fatal complications. It is emphasized to detect them quickly and commence accurate treatment. Novel therapies, such as exon-skipping gene therapies are expected to help alleviate the symptoms and slow down the progression of the disease.

Author's contribution

Conceptualization, Bartosz Mazur, Iwona Welian-Polus; methodology, Michał Bielak; software, Magdalena Mazur, Dawid Mika; check, Elżebieta Rypulak, Magdalena Mazur, Kamila Turek ; formal analysis, Michał Bielak; investigation, Magdalena Mazur, Karol Stachyrak; resources, Iwona Welian-Polus, Anna Greguła; data curation, Wiktoria Wilanowska; writing - rough preparation, Bartosz Mazur, Wiktoria Wilanowska; writing - review and editing, Iwona Welian-Polus, Michał Bielak, Dawid Mika; visualization, Michał Bielak; supervision, Elżbieta Rypulak, Anna Greguła; project administration, Bartosz Mazur, Kamila Turek; receiving funding, Magdalena Mazur

All authors have read and agreed with the published version of the manuscript.

Funding statement

The study did not receive special funding

Informed Consent Statement

Not applicable

Acknowledgments

Not applicable

Conflict of Interest Statement

The authors report no conflict of interest.

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