

# Severe course of dilated cardiomyopathy associated with Duchenne muscular dystrophy (RCD code: III-1A.3a)

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## Abstract

Inherited neuromuscular disorders, such as dystrophin-related disorders are frequently associated with cardiac involvement, mainly with cardiomyopathies. Dystrophin-related disorders are caused by the mutation in the dystrophin gene on the X chromosome. Two types of dystrophin-related disorders, namely, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) have been identified. DMD is a more severe form of muscular dystrophy. The cardinal symptoms of DMD are progressive skeletal muscle weakness and respiratory insufficiency due to the weakness of the respiratory muscle, which is the leading cause of premature death. Owing to the improvement in the general and respiratory care of DMD patients, associated cardiovascular abnormalities, mainly cardiomyopathies, are gradually becoming the main cause of comorbidity and mortality in these patients. We present a case of an 18 year-old male with DMD who developed heart failure with reduced ejection fraction due to dilated cardiomyopathy. Although the state-of-the-art treatment was initiated he eventually died from cardiopulmonary decompensation. Based on this case we provide thorough summary on the current knowledge on diagnosis and care of patients with DMD and heart failure. JRCO 2014; 2 (1): 18–22

**Key words:** cardiomyopathy, Duchenne muscular dystrophy, myopathy, neuromuscular disorder, genetics

## Background

Inherited neuromuscular disorders, such as dystrophin-related disorders, Emery–Dreifuss muscular dystrophy, facioscapulo-humeral muscular dystrophy, myotonic dystrophy, Friedreich's ataxia, and Barth syndrome, are frequently associated with cardiac involvement, mainly with cardiomyopathies.

Dystrophin-related disorders are caused by the mutation in the dystrophin gene on the X chromosome, which encodes dystrophin, a high-molecular-weight protein localized on the sarcolemmal membrane of the skeletal muscle. Two types of dystrophin-related disorders, namely, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) have been identified. DMD is a more severe form of muscular dystrophy than BMD and is characterized by the complete or almost complete lack of dystrophin in the skeletal muscles, whereas patients with BMD have an abnormal structure of dystrophin protein. These two types of muscular dys-

trophies also have different course of the disease. The first clinical manifestation of DMD, namely, muscle weakness, starts between the second and third year of age, whereas BMD develops later in life and its progression is much slower. In contrast, cardiac involvement can be more severe in BMD compared with DMD, which is partly explained by the fact that BMD patients can perform certain exercises, which could be an extra burden on the myocardial cells with already abnormal dystrophin.

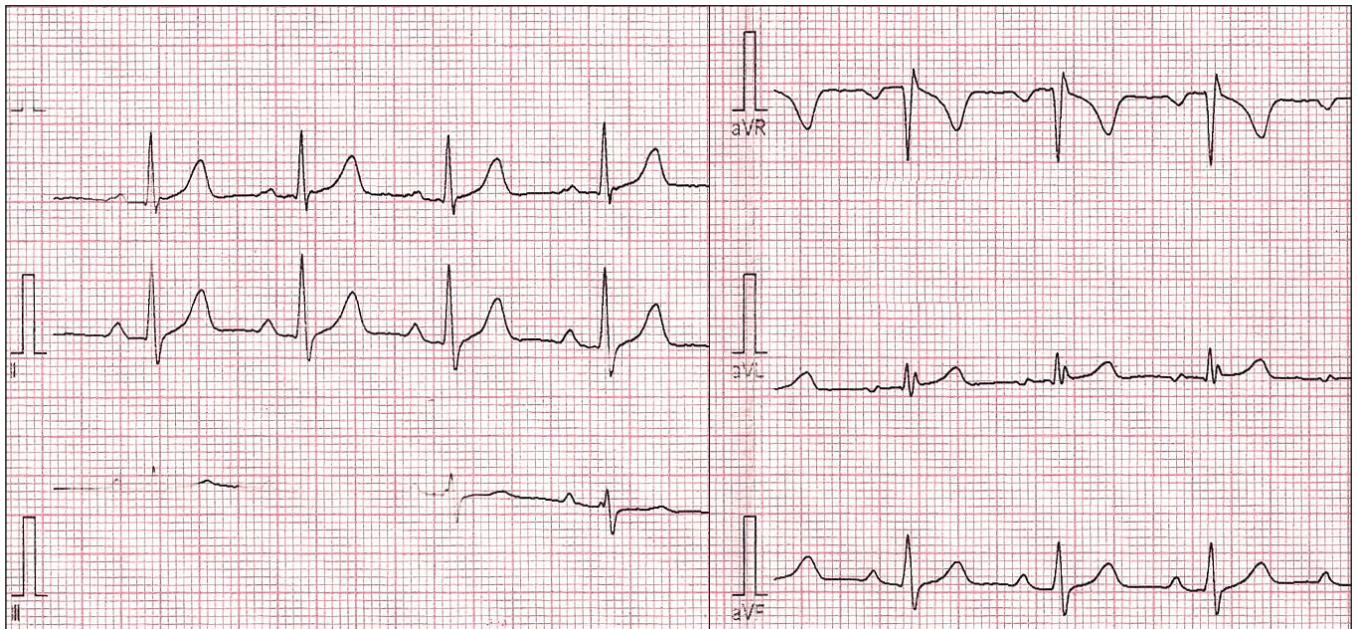
Only men develop the full spectrum of DMD symptoms, while women are carriers of dystrophin gene mutation. The cardinal symptoms of DMD are progressive skeletal muscle weakness, which eventually leads to complete loss of walking ability at the age of 10 to 12 years, and respiratory insufficiency due to the weakness of the respiratory muscle, which is the leading cause of premature death. Nowadays, advances in the treatment and rehabilitation of respiratory insufficiency, including mechanical ventilation, nocturnal ventilation, or spinal operation, allow patients to live longer with relatively preserved respiratory function. Owing to the im-

Conflict of interest: none declared.

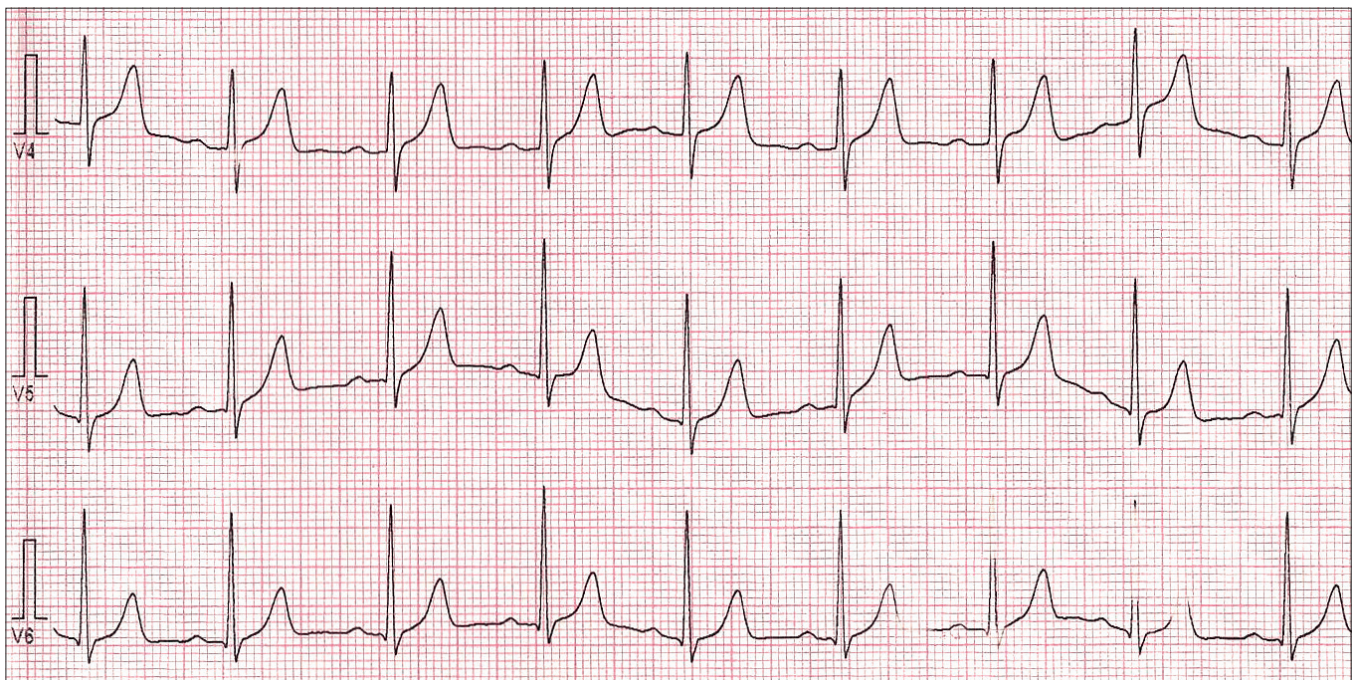
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**Figure 1.** Electrocardiogram. Sinus rhythm of 80 beats per min. Deep negative T waves in aVR



**Figure 2.** Electrocardiogram. Abnormally tall T waves in V4–V6

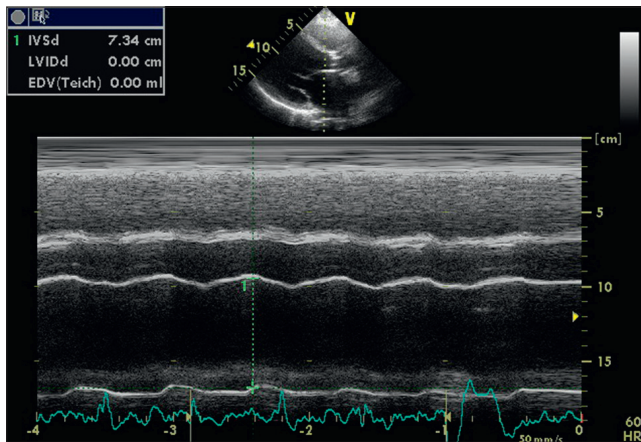
provement in the general and respiratory care of DMD patients, associated cardiovascular abnormalities, mainly cardiomyopathies, are gradually becoming the main cause of comorbidity and mortality in these patients [1].

This dramatic change in the landscape of muscular dystrophies is well reflected in the current guidelines for the diagnosis, monitoring, and treatment of concomitant cardiac disorders.

## Case presentation

An 18-year-old man with DMD was admitted to the Centre for Rare Cardiovascular Diseases in the John Paul II Hospital in Krakow because of progressive development of heart failure. He was diagnosed with DMD at the age of 2 years. He presented with enlarged calves, delayed walking, and difficulty in stair climbing. A genetic examination revealed deletion of 46–48 exons



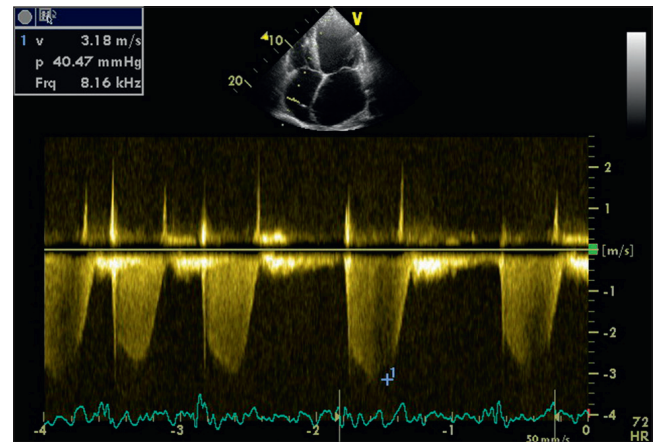


**Figure 3.** Transthoracic echocardiography. Severe dilatation of a hypocontractile left ventricle and left atrium

in the dystrophin gene (rod structure of the dystrophin gene), which confirmed DMD. At the age of 10 years, he became wheelchair-bound. At the age of 12 years, he underwent echocardiography for the first time, which revealed asymptomatic systolic insufficiency of the left ventricle. Treatment with an angiotensin-converting-enzyme inhibitor (ACEI, perindopril) was started. He remained under the care of the Institute of Pediatrics and, subsequently, when he reached the age of 18 years, he became the patient of the Congenital Heart Clinic of the John Paul II Hospital.

At presentation to the Centre, the patient's weight was 62 kg, his height was 156 cm, and the body mass index was 25.5 kg/m<sup>2</sup>. The patient did not report any cardiac symptoms, but he complained of fatigue and sleep disturbances. A physical examination revealed skeletal muscle weakness, a heart rate of 100/min, blood pressure of 110/70 mm Hg, audible third heart sound, and oxygen saturation of 96%. The respiratory rate was 19/min and the signs of fluid presence were heard in the inferior parts of the lung auscultation. No peripheral swellings or cyanosis were present. A standard 12-lead ECG revealed sinus tachycardia with a heart rate of 100/min, no deviated axis, abnormally tall R waves in leads V<sub>1</sub> through V<sub>3</sub>, and large Q waves in leads II, aVF, V<sub>5</sub>, and V<sub>6</sub> (Figure 1, 2). The levels of biochemical parameters such as hemoglobin, amount of erythrocytes, and liver function enzymes (ASpat, AlAt) were normal. A chest X-ray image showed the presence of fluid in the inferior parts of the lungs field and mild enlargement of the cardiopulmonary index (0.53). Echocardiography showed a dilated left ventricle with thinned wall and a significant decrease in the ejection fraction (20%); moderate mitral regurgitation was also observed (Figure 3, 4). So far, the patient has been treated with enalapril (5 mg/d), spironolactone (50 mg every 2 days), and digoxin (50 µg/d).

According to the current guidelines, patients with DMD older than 10 years should undergo echocardiography once a year. It allows to detect the development of a cardiac disorder. Our patient underwent his first echocardiography when he was 12-years old, and asymptomatic systolic insufficiency of the left ventricle was observed. He received perindopril and remained under the care of the Institute of Pediatrics, where he had been systematically monitored and his therapy modified accordingly. When he became the patient of



**Figure 4.** Transthoracic Continuous wave Doppler. Moderate tricuspid regurgitation with elevated right ventricle systolic pressure 55 mm Hg

the Congenital Heart Clinic of the John Paul II Hospital at the age of 18 years, he had advanced left ventricular cardiomyopathy.

During the next 6 months, his condition was rather good and he did not report any significant heart failure symptoms. Subsequently, he started to show more severe symptoms of a cardiac disorder, such as tachycardia with a heart rate of 100/min, peripheral swellings, and difficulty in breathing. He was prescribed a  $\beta$ -blocker. Echocardiography revealed a severely dilated left ventricle with pronounced spherical remodeling and secondary mitral regurgitation.

Despite optimal drug therapy, his condition gradually deteriorated until he suffered end-stage heart failure and died.

## Discussion

### Epidemiology

DMD is an X-linked disease that has an incidence of about 1 in 3500 male births, while BMD occurs in about 1 in 19 000 males [2]. The incidence of cardiomyopathy during the course of DMD increases with age. By the age of 6 years, almost one-quarter of DMD patients are diagnosed with cardiomyopathy, whereas in the next 4 years (until 10 years of age), almost two-thirds develop cardiomyopathy. Before reaching adulthood, almost all patients with DMD have concomitant cardiac involvement [3].

### Genetics

Both DMD and BMD result from the mutation of the gene encoding dystrophin protein, which is located within the band Xp21 on the X chromosome. The mode of DMD inheritance is recessive and X-transmitted; thus, the probability of passing the mutation to children is 50%, while the risk of having a sick son is 25%. Furthermore, almost 30% of DMD cases are caused by de-novo spontaneous mutations, which probably occurs during an ovary cell division [4].

Dystrophin is a membrane-associated cytoskeletal protein present in the skeletal and cardiac muscles, which forms a connection with the dystrophin-glycoprotein complex and has a crucial role in signal transduction [5]. In the absence of dystrophin, this con-

nection becomes destabilized, disrupting the integrity of the cellular membrane, and eventually leads to an increase in intracellular calcium content. The higher concentration of intracellular calcium ions activates the process of proteolysis causing muscle destruction. Damaged muscles are replaced with interstitial fibrosis and fatty tissue. In the heart, the degeneration of cardiomyocytes leads to fibrosis.

### Clinical manifestations

The intensity of clinical symptoms, course of the disease, and degree of skeletal muscle impairment depend on the type of muscular dystrophy. In DMD, where there is an absence of dystrophin, an early manifestation of disease is frequently observed. These patients show impaired mobility, with delayed walking and difficulty in stair climbing between the age of 2 and 4 years [2]. The enlargement of the calves is usually one of the first symptoms. On the contrary, patients with BMD, who have a reduced amount of dystrophin, have delayed onset of muscular weakness and overt symptoms. There are numerous muscles involved, including the proximal hip and shoulder girdle muscles, anterior neck, and abdominal muscles. In DMD, full-time use of a wheelchair is usually required between the age of 10 and 12 years. In the second decade of life, the impairment of the thorax muscles, responsible for the mechanism of breathing, becomes apparent, leading to progressive respiratory insufficiency. This severe complication is an ominous sign of the disease, requires highly-specialized medical care, including rehabilitation, passive and active breathing support, and so far has been the leading cause of death in these patients.

### Cardiac involvement

Cardiac involvement during the course of muscular dystrophies encompasses numerous abnormalities including various types of arrhythmias, dilated cardiomyopathy (DCM), intramural thickening of the coronary arteries, and persistent hypotension. The severity of a cardiac disorder may not parallel the severity of skeletal muscle disease. Overt DCM usually develops by the end of the second and the third decades of life in DMD patients, while the development of DCM in BMD patients is less predictable and may occur at any age. Although the echocardiographic phenotype of DCM is indistinguishable from DCM of other causes, there are certain characteristic features, which should always be considered in muscular dystrophies. First, even the basic assessment of the functional status by means of the New York Heart Association classification, is not feasible and or practical because the majority of patients are wheelchair-bound. Typical symptoms of the left- and right-ventricular congestion are rarely observed, while rather noncharacteristic symptoms of fatigue, weight loss, nausea, cough, heart palpitations, sleep disturbance, chest or abdominal discomfort, loss of appetite, decreased urinary output, or sweating should rise the suspicion of heart failure [2]. The “classic” cardiac symptoms such as chest pain, palpitations, dizziness, or syncope are usually manifestations of arrhythmias rather than heart failure. Unquestionably, a detailed history and examination of the patients and their caregivers play a fundamental role in early diagnosis of cardiac involvement in muscular dystrophies.

### Diagnosis of cardiac involvement

The current guidelines recommend a routine echocardiogram as the “gold standard” for early diagnosis of cardiomyopathy in DMD patients. Every patient should be examined by the age of 6-years old and have subsequent evaluations every 2 years until the age of 10 [6]. Thereafter, the echocardiogram should be repeated once a year. As early as in the second year of age, various cardiac abnormalities such as left ventricular dilatation, wall thinning, impairment of regional contractility, or secondary mitral regurgitation are frequently observed. These pathologies result from fibrosis of the posterior wall of the left chamber and later progress apically and laterally. Although an echocardiogram is an invaluable tool, there are some limitations specific for muscular dystrophies, which include gross kyphoscoliosis, wheelchair confinement, increased chest wall adiposity due to prolonged systemic steroid use. These inconveniences lead to technical difficulties in obtaining proper echocardiographic images. Thus, cardiovascular magnetic resonance imaging has become the additional diagnostic tool, which can be used to provide supplementary information about the structure and malfunctioning of the heart [7]. Moreover, late gadolinium enhancement identifies myocardial fibrosis and nonfunctioning myocardium [8].

### Prognosis

Life expectancy of DMD patients depends primarily on the natural progression of the disease and respiratory insufficiency. However, recent improvements in the treatment of respiratory muscle disorder allow patients to live longer with better respiratory function. The average lifespan is much longer than it has been earlier and, at present, most patients live until the third and even fourth decade of life [9].

### Treatment

According to the 2004 recommendations, the cornerstone of drug therapy in DMD are long-term oral steroids [10]. These recommendations were based on numerous studies which showed the beneficial effects of steroids on the skeletal and respiratory muscle function and progression of heart disease. Moreover, the current guidelines recommend early administration of ACEIs, which delay the progression of LV dysfunction and also decrease cardiac mortality in the long-term follow-up [11]. If ACEIs are not tolerated, alternatively angiotensin receptors blockers can be used. Additionally, adrenergic  $\beta$ -receptor blockade also proved valuable in the improvement of both cardiac symptoms and function. However, there is a paucity of rigorous scientific studies, especially those evaluating major mortality/morbidity endpoints. As in other areas of heart failure, neither diuretics nor digoxin provided any mortality benefits; nevertheless, they are frequently used to alleviate symptoms and eliminate congestion.

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