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A Rare Cause of Left Ventricular Dysfunction and Familial Dilated Cardiomyopathy in Children; Emery–Dreifuss Type 2: A Case Report

Çocuklarda Ailesel Dilate Kardiyomiyopatinin ve Sol Ventrikül Disfonksiyonunun Nadir Bir Nedeni; Emery–Dreifuss Tip 2: Olgu Sunumu

CASE REPORT
OLGU SUNUMU

ABSTRACT

Emery–Dreifuss muscular dystrophy is one of a group of muscular dystrophies caused by a deficiency in genes encoding nuclear proteins (emerin, lamin A/C, nesprin). It progresses with joint contractures, muscular dystrophy, and cardiac involvement. Cardiac findings include dilated cardiomyopathy, conduction defects, and an associated increased risk of sudden cardiac death. We report the case of a young boy, aged 16, with lamin A/C gene mutation and dilated cardiomyopathy. From the patient's history, it was learned that his father and sister also had dilated cardiomyopathy and both died of heart failure. Cardiac resynchronization therapy implantation was planned in the follow-up of the patient due to progressive left ventricular dysfunction and left ventricular dyssynchrony. But the family did not accept this treatment option. The patient was placed on the heart transplant list. While waiting for a suitable donor, he died as a result of sudden cardiac arrest while he was being treated in the intensive care unit.

Keywords: Cardiomyopathy, dyssynchrony, Emery–Dreifuss muscular dystrophy, genetics

ÖZET

Emery-Dreifuss müsküler distrofisi, nükleer proteinleri (emerin, lamin A/C, nesprin) kodlayan genlerdeki eksiklikten kaynaklanan bir grup müsküler distrofiden biridir. Eklem kontraktürleri, müsküler distrofi ve kalp tutulumu ile ilerler. Kardiyak bulguları; dilate kardiyomiyopati, iletim kusurları ve artmış ani kardiyak ölüm riskini içerir. Burada Lamin A/C gen mutasyonu ve dilate kardiyomiyopatisi olan 16 yaşında genç bir erkek olgu sunulmaktadır. Hastanın öyküsünden babası ve ablasında da dilate kardiyomiyopati olduğu ve her ikisinin de kalp yetersizliğinden kaybedildiği öğrenildi. Hastanın takibinde ilerleyici sol ventrikül disfonksiyonu ve sol ventrikül dissenkronisi olması nedeniyle kardiyak resenkronizasyon tedavisi implantasyonu planlandı. Ancak aile bu tedavi seçeneğini kabul etmedi. Hasta kalp nakli listesine alındı. Uygun bir donör beklerken yoğun bakım ünitesinde tedavi altındayken ani kardiyak arrest gelişmesi sonucu kaybedildi.

Anahtar Kelimeler: Emery-Dreifuss müsküler distrofisi, dissenkroni, genetik, kardiyomiyopati

Emery–Dreifuss muscular dystrophy (EDMD) is an inherited neuromuscular disease characterized by joint contractures, slowly progressive muscle weakness, and cardiac problems. Cardiac involvement includes atrial arrhythmias, conduction defects, cardiomyopathy, and congestive heart failure.[1] These clinical manifestations are caused by mutations in the genes encoding nuclear proteins. Besides X-linked recessive inheritance, autosomal dominant and autosomal recessive inheritance has also been reported, and they are associated with heart failure, arrhythmias, and cardiomyopathy. Sporadic inheritance of the disease has also been identified. Additionally, the lamin A/C (LMNA) gene mutation is observed in EDMD type 2.[2]

Here, we report the case of a 16-year-old adult patient with a positive LMNA gene mutation. The patient who was recommended cardiac resynchronization therapy (CRT) implantation because of progressive left ventricular dysfunction and dyssynchrony

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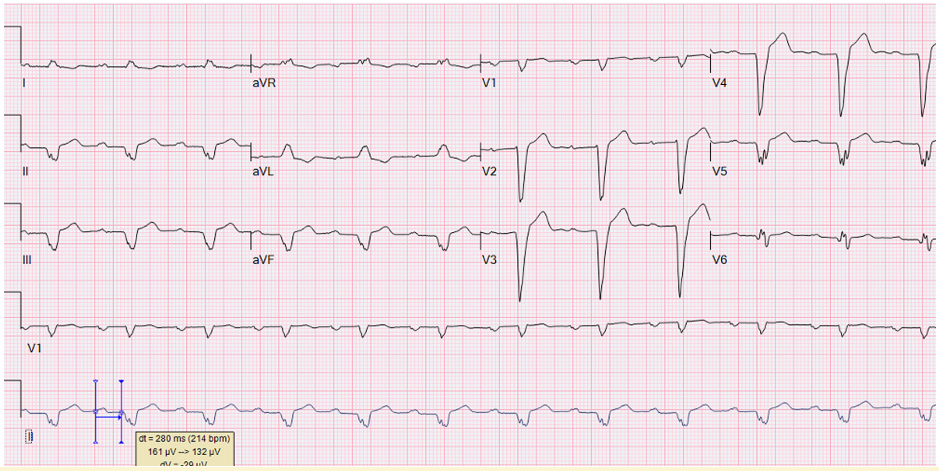

Figure 1. Baseline ECG showing sinus rhythm and first-degree atrioventricular block (PR interval 280 ms), left axis deviation and intraventricular conduction delay with wide QRS (QRS duration 156 ms). ECG: 10 mm/mV, 25 mm/s. ECG, electrocardiogram.

died in the intensive care unit following the development of sudden cardiac arrest.

Case Report

A 16-year-old male patient was admitted to our clinic with complaints of peroneal muscle weakness and fatigue. There was no consanguinity between the mother and the father. His father died at the age of 33 due to heart failure caused by muscular dystrophy, although he had an intracardiac defibrillator (ICD). He lost his sister at the age of 17 years due to muscular dystrophy, like his father, and she also had an ICD. The patient had no other siblings. TruSight One next-generation sequencing panel was used for genetic analysis. The results confirmed the diagnosis of EDMD type 2 by identifying the mutation c.G746A in the LMNA gene. The patient's family was informed about the hereditary transmission of the disease, and genetic counseling was provided. It was noted that the patient could continue with his normal daily activities, except for his current complaints, and he had no history of palpitations or syncope. Weakness in the peroneal muscles and fatigue were the only findings on physical examination. A grade 3 systolic murmur was detected in the apical region upon cardiac auscultation.

Laboratory examination revealed that creatinine kinase enzyme was 17.06 ng/mL (0-6.22), troponin T level was 674 ng/L (0-14), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level was 2112 pg/mL (0-125). His thyroid hormone levels were normal. Electrocardiography (ECG) showed sinus rhythm, first-degree atrioventricular block (AVB) (PR duration: 280 ms), left-axis deviation, and intraventricular conduction delay with wide QRS (156 ms) and normal corrected QT interval (440 ms) (Figure 1). Ambulatory ECG examination demonstrated sinus rhythm, with minimum, mean, and maximum heart rates of 36, 82, and 112 bpm, respectively, and periods of first-degree AVB. Frequent supraventricular extrasystoles were also detected, with rare episodes of supraventricular tachycardia and infrequent polymorphic ventricular extrasystoles. In addition, it was occasionally observed that the QRS duration was extended, particularly when the heart rate increased. Telecardiogram indicated cardiomegaly (Figure 2A).

Echocardiography revealed left ventricular dilatation, left ventricular systolic and diastolic dysfunction, and left ventricular mechanical dyssynchrony. (Figure 2B). Dyssynchrony measurements indicated that the time difference for intraventricular dyssynchrony between the maximal systolic inward movement of the septal and posterior (lateral) wall was 300 ms (normally <130 ms). Additionally, for interventricular dyssynchrony, the difference between pulsed-wave Doppler echocardiography and aortic and pulmonary pre-ejection intervals was 95 ms (normally <40 ms). Atrioventricular dyssynchrony was not observed (>50%). The left ventricular end-diastolic diameter was 60 mm (z score: +2.47), and the left ventricular ejection fraction (LVEF) was 30%-32%. Moderate mitral valve regurgitation was observed.

Cardiac magnetic resonance imaging revealed movement defects consistent with hypokinesia on all surfaces of the left and right ventricles. Hypokinesia was more prominent, particularly in the middle and apical parts of the left ventricle (LV).

Cardiac resynchronization therapy-defibrillator (CRT-D) implantation was recommended for the patient because of severe left ventricular dysfunction, premature ventricular beats, and LV mechanical dyssynchrony. There were cases with a family history of this disease. The patient's family did not accept this treatment option. Therefore, the patient was enrolled on a heart transplant list. However, the family declared that the patient died in another central intensive care unit following sudden cardiac arrest.

ABBREVIATIONS

AVB	Atrioventricular block
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy- defibrillator
DCM	Dilated cardiomyopathy
ECG	Electrocardiography
EDMD	Emery–Dreifuss muscular dystrophy
ICD	Intracardiac defibrillator
LMNA	Lamin A/C
LV	Left ventricle
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal prohormone of brain natriuretic peptide

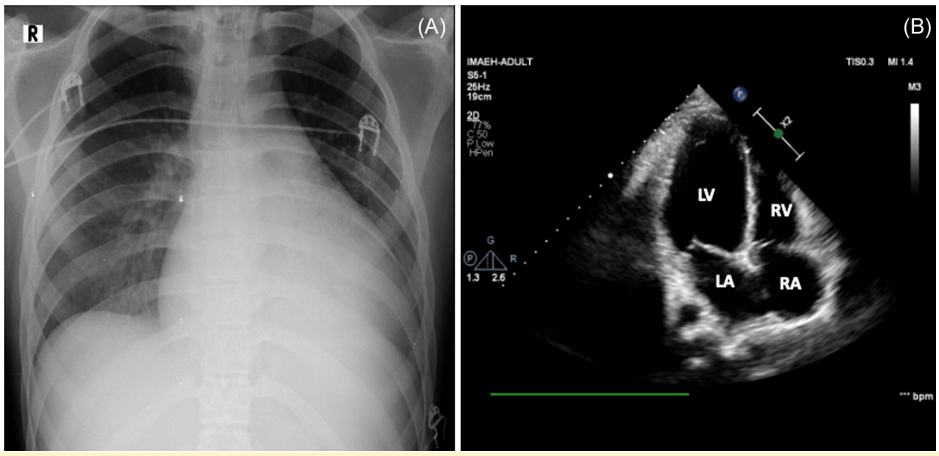

Figure 2. A-B. (A) Telecardiogram indicating cardiomegaly, cardiothoracic index was >0.65. (B) Transthoracic echocardiography pointing out cardiac dilatation. The left ventricular end diastolic diameter was 60 mm, and the left ventricular ejection fraction was 30%-32%. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Discussion

Emery–Dreifuss muscular dystrophy is a chromosome-X-linked transmitted emerin deficiency. It is typically characterized by muscle weakness; contractures affecting the Achilles tendon, elbows, and spinal muscles; and cardiac manifestations. Cardiac findings included palpitations, syncope, heart failure, ventricular or supraventricular arrhythmias, conduction disorders, dilated/hypertrophic cardiomyopathy, and sudden death.[3] In 1999, an autosomal dominant inherited type due to LMNA mutations was identified: EDMD type 2. Cardiac and skeletal muscle involvement can vary even among family members with LMNA gene mutations. This suggests that different genetic modifiers are effective in the genetic expression of the disease.[4] Lamin A/C mutations may be clinically more severe than X-linked EDMD mutations, with more severe cardiac involvement and an earlier age of onset.

The LMNA gene encodes the lamin A/C protein, which can damage the nuclear membrane and cause cardiac conduction disturbances. This gene variant is also associated with sudden cardiac death and life-threatening arrhythmias.[5] Progressive conduction system defects with cardiac dilatation can be observed as an initial or unique clinical manifestation of the disease.[2] The cardiac features of EDMD have been characterized as supraventricular arrhythmias (atrial premature contractions, atrial tachycardia, atrial fibrillation, and atrial standstill), atrioventricular conduction disturbances (AVB of any degree), and ventricular arrhythmias (ventricular premature contractions, ventricular arrhythmias, ventricular tachycardia dysfunction, and left ventricular enlargement). In addition, dilated cardiomyopathy (DCM), restrictive cardiomyopathy, and sudden death despite pacemaker implantation have been described as well.[3] Nuclear damage in cardiac myocytes rapidly accumulates and determines the faster progression of the dysfunction of conductive and contractile cells.[6] Therefore, cardiac conduction disorders are rapidly progressing.

In a study comparing emerinopathy and laminopathies, laminopathies were associated with ventricular arrhythmias at a higher rate. For AVB, the mean age was found to be relatively higher in laminopathies (32.8 +/– 10.6 vs 25.1 +/– 9.1).[7] In our case, a first-degree AVB was detected at the first admission when the patient was only 16 years old. During follow-up, atrial and ventricular premature beats were observed on the ECGs in addition to first-degree AVB. The patient's conduction disorder and premature beats developed earlier than those reported in the literature. Furthermore, sudden death can occur at any stage of follow-up. Therefore, close cardiac follow-up from the onset of diagnosis is very important.

Permanent pacemaker implantation for patients with LMNA gene mutations with LVEF between 36% and 50% and any degree of AVB are recommended. The most recent guidelines provide a class IIa recommendation for the use of pacing methods that maintain physiological ventricular activation in patients with an LVEF between 36% and 50% who are expected to require ventricular pacing more than 40% of the time. It has also been reported that adding a defibrillator to permanent cardiac pacing as needed provides significant survival longer than 1 year, as expected.[8] Cardiac conduction disorder caused by the LMNA gene variant is considered progressive; therefore, biventricular pacing treatment will be indispensable.[5] According to the 2021 The Pediatric & Congenital Electrophysiology Society (PACES) guidelines, permanent pacemaker implantation is reasonable in patients with a PR interval >240 ms and/or left bundle branch block and LMNA gene mutations, including limb-girdle and EDMD. Additional defibrillator capabilities may be considered.[9] In our patient, permanent pacemaker indication was also present because of LMNA gene mutation and PR interval >240 ms. He had a LVEF <50% and left ventricular dyssynchrony. CRT-D implantation is recommended for physiological pacing and the prevention of heart failure. However, the patient and his family did not accept this treatment option.

There is no specific treatment for EDMD type 2. Although permanent pacemaker implantation reduces the risk of sudden cardiac death, there have been reports of sudden death even after pacemaker implantation.[10] The patient's father died at 33 years of age, although he had an ICD. His muscle weakness advanced,

and he was unable to walk. Similarly, his sister died when she was 17 years old and she also had an ICD. The patient had mild muscle weakness. The treatment of heart failure is recommended in complicated cases of DCM. Heart transplantation is a realistic option in resistant cases.

Here, we report a rare familial EDMD type 2 patient with left ventricular dyssynchrony and DCM, who also had first-degree AVB and permanent pacemaker indication due to the LMNA gene. Any degree of AVB can progress rapidly, particularly in patients with left ventricular dysfunction and heart failure. Emery–Dreifuss muscular dystrophy type 2 may also cause fatal ventricular arrhythmias and sudden cardiac death. Therefore, these patients should be followed-up closely in terms of permanent pacemaker implantation and the need for heart transplantation.

Informed Consent: Written informed consent was obtained from the patient's family for the publication of the case report and the accompanying images.

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Author Contributions: Concept - E.D., Y.E.; Design - E.D., A.S.; Supervision - H.C.K., Y.E.; Materials - E.D., H.C.K.; Data Collection and/or Processing - E.D.; Analysis and/or Interpratation - A.S., Y.E.; Literature Review - E.D., A.S., H.C.K.; Writing - E.D., A.S.; Critical Review - H.C.K., Y.E.

Declaration of Interests: The authors declare that they have no competing interest.

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