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CASE REPORT

Hypertrophic Cardiomyopathy and Arrhythmias as Phenotype Spectrum of Emery Dreifuss Muscular Dystrophy: First Case Report in Bahrain

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Abstract

Muscular dystrophies are a heterogeneous group of inherited disorders characterized by progressive wasting and weakness of the skeletal muscles. The clinical spectrum ranges from early presentation with severe clinical features in childhood to onset in adulthood with less severe clinical symptoms and slow progression. This frequently raises difficulties in diagnosis. The predominant features may be cardiac, and this may lead to a complex diagnosis.

Emery Driefuss Muscular dystrophy (EDMD) is a rare form of limb girdle muscular dystrophy. The prevalence is less than 1:100,000 individuals. The condition may be associated with significant muscular cardiac abnormalities which is responsible for mortality in these patients.

The authors describe a case of hypertrophic cardiomyopathy in which limb girdle muscular dystrophy was suspected and subsequently confirmed by genetic studies as part of the phenotypic spectrum of X-linked EDMD. This is the first diagnosed case of EDMD in Bahrain.

Keywords: Bahrain, Hypertrophic Cardiomyopathy, Limb-girdle muscular dystrophies, Muscular dystrophies, Skeletal muscles

Introduction

Emery Dreifuss is a very rare genetic X-linked cardiomyopathy associated with skeletal muscle and cardiac muscle involvement with significant consequences for the patient. The authors present the first case of Emery Dreifuss cardiomyopathy diagnosed in Bahrain.

Case report

A 47-years old male was referred for coronary angiography. The patient had attended the referral center, complaining of dyspnea on exertion and atypical, pricking chest pain with no relation to exertion and no other anginal features. There was no history of palpitations or loss of consciousness. The patient was diagnosed of asthma at the local

health center and inhalers had been prescribed in the past but no formal assessment for reversible bronchospasm had been done. The patient was not diabetic or hypertensive. Dyslipidemia was noted in the past and he was taking statins. There was a history of cigarette smoking and no alcohol intake. There was a history of hip surgery in childhood said to be due to congenital hip dislocation and revision of hip surgery in 2007. No operative details were available.

Computed tomography (CT) of the coronary arteries was done at another center in 2005 which was reported normal, but no record was available. There was a history of recurrent pleural effusion which was investigated twice at another center but no final diagnosis made. Additionally, report of a myocardial perfusion imaging scan showed a partially reversible myocardial perfusion defect. Echocardiogram was reported normal at the referral center.

History at the initial visit at Mohammed bin Khalifa bin Salman al Khalifa Specialist Cardiac Centre was consistent with the referral details i.e., intermittent atypical chest pain since 2005 with no anginal features, dyspnea on exertion New York Heart Association class 11, no cough or wheeze and no improvement with inhalers.

Family history revealed that the patient's brother had the same phenotypical features and had an undiagnosed cardiac problem for which he had not been investigated. There was no other known history of muscular dystrophy, cardiac problems, or sudden cardiac death in the family. Consanguinity of the patient's parents was reported, and the patient is married to his cousin. The patient has four children, two daughters and two sons, all of whom are apparently healthy. The patient was independently mobile with a waddling gait and held down a regular job. Systems review was otherwise negative apart from complaints of poor vision which has not been formally investigated.

Medications at the time of referral were aspirin 81mg daily, bisoprolol 2.5mg daily, atorvastatin 20mg daily, trimetazidine 35mg twice daily, Symbicort inhaler and regular salbutamol inhaler.

On general examination, weight was 63.0 kg with blood pressure (BP) 141/65 mmHg, heart rate 84 bpm with regular rhythm. Physical examination revealed abnormal facies, down slanting palpebral fissures, and ptosis of the left eyelid. Previous scars of lymph node biopsies in the neck was observed. The thyroid was normal.

Examination of the cardiovascular system was normal. The jugular venous pressure was not elevated, no carotid bruits were audible, normal position of the apex beat with no right ventricular (RV) heave and no murmurs audible. Examination of the respiratory system and abdomen were normal.

There were physical findings consistent with possible limb girdle muscular dystrophy on examination - low shoulders, slanting downwards with winged scapula but only mild muscle weakness in the upper limbs. There was significant limitation of external rotation of the left hip, the left foot appeared larger and wider than the right and had limitation of eversion. There was no objective evidence of muscle weakness in the lower limbs. Neurological examination was normal apart from mild muscle weakness.

In view of the history and the clinical examination, the diagnosis at the initial visit was possible Limb Girdle Muscular Dystrophy (LGMD) and relevant investigations were pursued to evaluate a possible cardiac involvement and clarify the diagnosis.

Electrocardiogram (ECG) at the first presentation showed normal sinus rhythm, normal axis, Left Ventricular Hypertrophy (LVH) with strain pattern noted. Routine blood work showed the following: Complete blood count normal, mild elevation liver function tests and bilirubin. Erythrocyte sedimentation rate was 30mm/1st hour. Mild elevation creatine phosphokinase = 382 IU/l, thyroid function tests normal. Lipids - low density lipoprotein = 2.52mmol/l on statins.

Chest X-ray was normal with no pleural effusion. Transthoracic echocardiography revealed the following: Dilated Left atrium with volume 70 ml. Normal left ventricular end diastolic dimension. There was significantly increased left ventricular wall thickness in concentric remodeling fashion. Maximum wall thickness was 1.6cm, relative wall thickness 0.63cm and LV mass =198 grams

(Figure 1). There was significant papillary muscle hypertrophy. There was abnormal orientation of papillary muscle with anterior displacement. Small thinned out area in apical septum with incomplete obliteration in systole. No regional wall motion abnormalities at rest.

Restrictive diastolic dysfunction with raised LV filling pressures with mitral valve early filling peak velocity (E) to early diastolic mitral annulus (e') velocity (E/e') 13, and pulmonary wedge pressures (PCWP) =17.8mmHg. The aortic valve was tricuspid and opened normally. There was no aortic regurgitation. The mitral valve was also normal in structure and function. The tricuspid valve was structurally normal with trivial tricuspid regurgitation and estimated systolic pulmonary artery pressure (SPAP) = 24mmHg. The pulmonary valve was normal. Normal Ascending aorta size. The right ventricle was normal in size and systolic function with tricuspid annular plane systolic excursion (TAPSE)=1.6cm, Right ventricle (RV) free wall tricuspid peak systolic velocity (PSV) by tissue Doppler imaging (TDI) 11.1cm/s. Only mild increase in RV wall thickness was reported. The inferior vena cava (IVC) size was normal with normal respiratory variations.

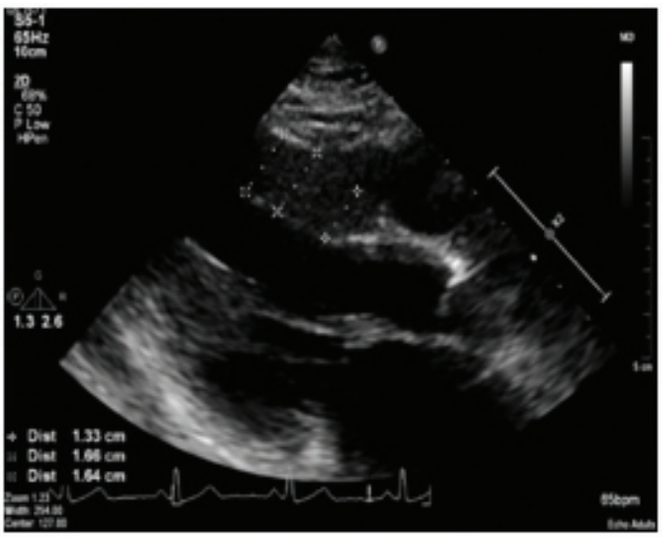

Figure 1: TTE showing septal hypertrophy

Contrast perfusion scanning showed normal uptake in all the segments except for a small area in the apical segment. Contrast enhanced left ventricular ejection fraction (LVEF) was 79% with end diastolic/end systolic volume (ED/ESV) = 66/14ml. Global longitudinal peak systolic strain was 17% with reduced segmental strain in mid to base lateral and posterior walls and basal septal segments (Figure 2).

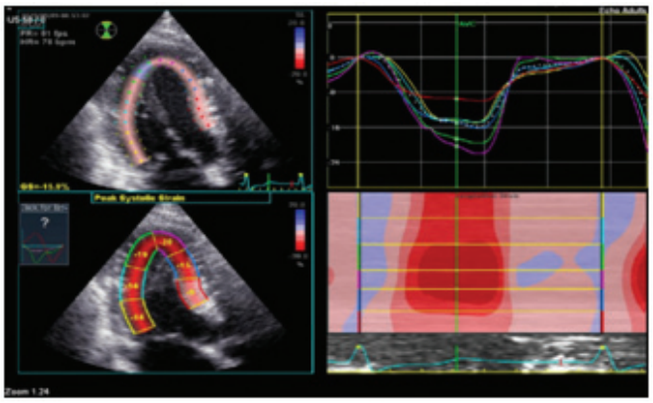

Figure 2: Peak systolic strain

Features of the physical examination such as, mildly increased creatine phosphokinase serum level, and the echocardiogram appearance (increased LV wall thickness with bright appearance) supported the possibility of cardiac involvement- Hypertrophic Cardiomyopathy- associated with a limb girdle muscular dystrophy.

Although coronary artery disease was felt to be unlikely, CT Angiography of the coronaries was repeated (Figure 3) and showed normal coronary arteries.

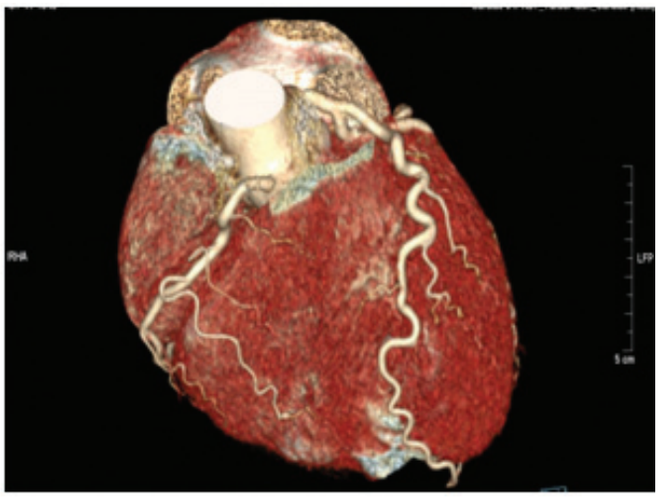

Figure 3: Cardiac CT – volume rendered images

24-hour blood pressure (BP) monitoring was done in view of the initial high BP and to exclude hypertension as a cause of left ventricular hypertrophy. This was normal.

Cardiac magnetic resonance scanning (CMR) with gadolinium enhancement confirmed thickened myocardium with a small area of enhancement in the apex indicative of myocardial fibrosis and consistent with nonobstructive hypertrophic cardiomyopathy (Figure 4).

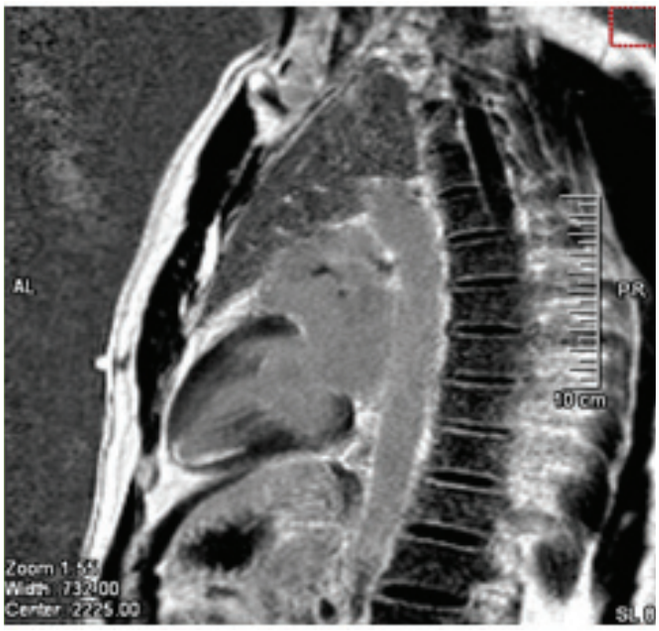

Figure 4: Late Gadolinium Enhancement magnetic resonance imaging a showing small area of myocardial fibrosis

Continuous ambulatory ECG monitoring (Holter) showed ventricular arrhythmias i.e., 86 isolated ventricular ectopic beats (VE's), 2 couplet episodes, no bigeminy or trigeminy and a short episode of non-sustained ventricular tachycardia. 316 isolated supraventricular (SV) ectopics, 19 couplets and 25 short runs of non-sustained SV tachycardia. There were episodes of sinus bradycardia with minimum rate of 36 bpm during sleep. There was no heart block.

Investigations were consistent with cardiac involvement (cardiomyopathy, arrhythmias) of a limb girdle muscular dystrophy. Genetic studies were considered for a precise diagnosis. The patient gave a signed written consent and was included in a research program of inherited cardiomyopathies comprehensive genetic investigation (Arabian Gulf University Grant E016-Pi-11/18). A cardiomyopathy comprehensive next generation sequencing (NGS) panel testing (Invitae, USA) was performed. The genetic testing reported that our patient is hemizygous for a likely pathogenic variant c.688+1G>C in FHL1 gene. The genotype correlates with the clinical phenotype, confirming a rare type of limb girdle muscular dystrophy and establishing the diagnosis of X-linked Emery Dreifuss muscular dystrophy (EDMD).

In view of the clinical and echo findings, the patient's dyspnea on exertion is likely to be the result of cardiomyopathy and diastolic dysfunction rather than asthma. The patient will be monitored closely for the progression of heart failure and arrangements have been made for device therapy in view of the high incidence of sudden cardiac death (SCD). Permanent pacemaker implantation (PPM) is usually advised in view of the high risk of conduction abnormalities but recently, following documentation of SCD in patients with EDMD despite PPM implantation, automated implantable cardiac defibrillator (AICD) rather than PPM will be implanted in our patient.

Discussion

Emery Dreifuss muscular dystrophy (EDMD) is a very rare genetic disorder. It is slowly progressive and affects muscles of the arms, legs and heart resulting in variable clinical consequences for the patient depending on phenotypic expression. The most common form of EDMD is the autosomal dominant form which is caused by mutations in LMNA gene (1q21.2). This patient was diagnosed with the rarer X-linked form of EDMD - caused by mutations of the EMD gene (Xq28) or FHL1 gene (Xq26.3). Mutations in FHL1 gene are responsible for approximately 2.5% of cases of EDMD.

The onset and progression of clinical abnormalities of EDMD varies widely. The condition is often overlooked and often not diagnosed until later in life. Cardiac involvement usually presents from the second decade of life onwards. Respiratory function may be impaired in some individuals.[1] The classical cardiac findings of EDMD are those of hypertrophic cardiomyopathy with diastolic dysfunction. Arrhythmias such as bradycardia and heart blocks or ventricular arrhythmias are also a feature. Some patients may demonstrate cardiac involvement without muscular features. In addition, cardiac abnormalities including cardiomyopathy and conduction and rhythm abnormalities can be seen with only mild muscle involvement and 10-20% of female carriers of X-linked EDMD show cardiac conduction abnormalities.[2] Sudden cardiac death has been reported in the literature in patients without definite muscular involvement.[3] This patient had the classical findings of this type of limb

girdle muscular dystrophy but muscle weakness was mild and he remains independently mobile and indeed, loss of mobility is rare in the X linked variant of EDMD. Cardiac features, however, were prominent and are what would limit longevity without recognition and treatment.

This patient exhibited both marked bradycardia and short runs of non-sustained ventricular tachycardia and may benefit from implantation of AICD. Long term prognosis is dictated by the cardiac abnormalities so detailed clinical assessment, full and complete investigations including genetic studies are essential.

Screening of relatives is paramount and will be carried out in the case of our patient. Establishing a genetic diagnosis is crucial for genetic counselling and treatment of cardiomyopathy and arrhythmias, to prolong life and improve the quality of life for patients.[4]

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Conflict of Interest

No conflict of interest for any party.

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