Role of an Implantable Cardioverter Defibrillator in Emery Dreifuss Muscular Dystrophy: A Case Report and a Review of the Literature

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Abstract

Emery dreifuss muscular dystrophy (EDMD) is one of the three most common inherited muscular dystrophies characterized by a triad of contractures, muscle weakness, and cardiac involvement (conduction abnormalities and/or cardiomyopathy). It can be inherited as X-linked recessive, autosomal dominant or autosomal recessive pattern. Cardiac involvement is evident in virtually all cases by the end of 4th decade. There is no relationship between the severity of cardiac and skeletal muscle involvement, irrespective of the mode of inheritance and type of mutations. Sudden death is a major cause of mortality in EDMD patients. Currently there is no definitive treatment for EDMD. Although permanent pacemaker implantation is a part of guidelines for cardiac conduction abnormalities associated with EDMD, it does not seem to prevent sudden death. Although implantable cardioverter defibrillator (ICD) is not currently recommended for EDMD patients without cardiomyopathy who otherwise do not meet the criteria for ICD, several lines of evidence suggest that sudden death can be prevented by an early ICD implantation in EDMD patients. We present a rare case of EDMD with significant cardiac conduction abnormality without any major skeletal muscle involvement detected at the age of 65 years, in whom ICD proved to be life saving. We also review the literature regarding the role of ICD in EDMD patients.

Keywords

Emery dreifuss muscular dystrophy; Sudden cardiac death; Defibrillator

Introduction

Emery-Dreifuss muscular dystrophy (EDMD) is one of the three most common type of muscular dystrophies characterized by the clinical triad of i) contractures of the elbows, ankles, and posterior neck; ii) slowly progressive muscle weakness and wasting in a scapula-humeroperoneal distribution; and iii) cardiac conduction defects, cardiomyopathy, or both [1]. EDMD was first described in 1966 by Emery and Dreifuss as an unusual type of benign X-linked muscular dystrophy [2]. It was later designated as Emery-Dreifuss type in 1979 by Rowland et al. [3]. Cardiac involvement without major musculoskeletal involvement is rare. Cardiac manifestations can range from sinus bradycardia, atrio-ventricular conduction abnormalities, atrial paralysis, atrial as well as ventricular arrhythmias, and cardiomyopathy as the disease progresses [1,2]. Sudden death is a major cause of mortality in EDMD patients [4,5]. An implantable cardioverter defibrillator (ICD) is not currently indicated for EDMD patients who otherwise do not meet criteria for ICD. We describe a rare case where cardiac involvement was seen at a very late age without any significant muscular involvement, and ICD proved to be life saving. We also discuss the role of ICD in EDMD.

Case Report

A 65 year old Caucasian male was referred to our hospital in March 2011 after a regular check up at the clinic showed slow heart rate on the Electrocardiogram (ECG). He did not have any dizziness, loss of consciousness, chest pain, shortness of breath or palpitations, neither at rest nor on exertion. He also denied any recent illness, sick contacts or recent travel. The patient’s past medical history was significant only for well controlled hypertension and dyslipidemia. He had been otherwise healthy throughout his life but reported to have difficulty climbing stairs recently. The patient had a strong family history of Emery Dreifuss Muscular Dystrophy (EDMD) with three sisters, one brother and two nephews (both sons of one of the sister) being diagnosed with EDMD. All three sisters had pacemaker implanted for conduction abnormalities and the brother had an Implantable Cardioverter Defibrillator (ICD) placed after surviving a sudden cardiac arrest. Mutations in genes coding for both Emerin and Lamin A/C were found in the affected family members. The patient had a previous ECG done a year ago in the primary physician’s office with normal heart rate and 2nd degree Mobitz type 1 AV block. Initial physical examination on this visit was benign except for bradycardia and mildly decreased muscle strength in lower extremities. The current ECG showed a heart rate of 37 beats per minute with evidence of ectopic atrial rhythm, atrial bradycardia and 2nd degree Mobitz type 1 AV block (Figure 1). A transthoracic echocardiogram showed a left ventricular ejection fraction (EF) of more than 55%, normal chamber size for atria and ventricles, mild mitral and tricuspid regurgitation, aortic sclerosis and mitral annular calcification. Telemetry monitoring in the hospital showed repeated evidence of marked bradycardia up to 30 beats per minute with ectopic atrial
activity and 2nd degree AV block. The genetic testing was sent which subsequently revealed heterozygous missense mutation 1129C>T nucleotide change in the LMNA gene. The diagnosis of autosomal dominant EDMD was made and the patient was discharged home after placement of an implantable cardioverter defibrillator (ICD). He follows up regularly at the hospital’s cardiology clinic. In April 2013, his ICD interrogation showed an episode of sustained ventricular tachycardia (VT), which was terminated by anti-tachycardia pacing (Figures 2-4). His EF was normal at that time as well.

Review of Literature

EDMD is most commonly inherited as X-linked recessive, but autosomal dominant and rare autosomal recessive modes of inheritance have also been described. The disease frequency is estimated to be 1/100000 for the X-linked form but is unknown for the other two forms [6]. The gene for X-linked form was identified as STA on chromosome Xq28, which codes for the protein emerin [7]. Bonne et al. proved that mutations in LMNA gene located on chromosome 1q11-q23, which codes for lamin A/C proteins were responsible for autosomal dominant form. So far, around 100 mutations in the STA gene and 32 mutations in LMNA gene causing EDMD have been reported [8].

Emerin, an inner nuclear membrane protein, is ubiquitously found in all somatic cells and serves to stabilize the nuclear membrane against the mechanical stresses generated in muscle cells during contraction. Lamins A and C are members of type V intermediate filament. They play a role in DNA replication, chromatin organization, spatial arrangement of nuclear pore complexes, nuclear growth, and mechanical stabilization of the nucleus and anchorage of the nuclear envelope proteins [6]. Even though these proteins are expressed in all the somatic cells, the reason for EDMD affecting cardiac muscle and certain skeletal muscle groups is unclear. Various hypotheses like mechanical stress hypothesis, gene expression hypothesis, abnormalities in cell proliferation or differentiation have been proposed as pathogenesis of EDMD but none of them have been able to explain the disease process completely [9].

Contractures are usually the first clinical sign of the disease and appear before muscle weakness and wasting. The slowly progressive muscle weakness and wasting begins in a humeroperoneal distribution, usually by the end of second decade of life. Cardiac involvement with EDMD is the most concerning feature of the disease. Cardiac disease occurs in virtually all cases of EDMD, in most cases, symptoms begin at the end of second decade [9]. Atrial conduction defects are considered to be the hallmark of the disease and atrial paralysis is almost pathognomonic of EDMD [10,11]. Four main features of cardiac involvement have been described in EDMD: i) impairment of impulse generating cells, ii) variable sinoatrial and atrioventricular conduction defects, iii) increased atrial and ventricular heterotopias, and iv) functional impairment of the ventricular myocardium [8]. Cardiac manifestations include conduction abnormalities including sinus bradycardia, varying degrees of AV blocks, tachyarrhythmias like atrial flutter, atrial fibrillation, ectopic atrial tachycardia, and ventricular tachycardia. A variety of atrial dysrhythmias occur as disease progresses in the fourth decade in almost every patient, and heart failure follows two decades later [4,10,12].

Although cardiac involvement usually occurs in the second decade and after skeletal muscle involvement, it is not always the case.
Involvement of the heart as early as 5 years has been seen and it has also been reported to occur without any prior muscle involvement. Furthermore, cardiac manifestations have been shown to progress unpredictably [12-14]. Cardiac involvement can occur as late as in the 60’s as was seen in our patient. Even though the clinical features of X-linked and autosomal dominant forms are similar, there are certain differences. There is more heterogeneity in the skeletal muscle involvement, increased incidence of isolated cardiac involvement, frequent progressive evolution of cardiac dysfunction, and increased severity of muscle weakness in autosomal dominant form [12,14]. There has been no correlation between cardiac and skeletal muscle involvement [12]. Also there has not been a clear relation between the type of mutation and the phenotype. Mutations in both rod domain and the tail of LMNA gene can give rise to cardiac manifestations unlike previously thought. Also, a same mutation of LMNA gene was found to give the clinical picture of EDMD, dilated cardiomyopathy with conduction defects, and limb girdle muscular dystrophy. Thus, some consider them as one disease entity with variable expression of symptoms [9,14]. There is also a significant interfamilial and intrafamilial variability reported [10,14].

In addition, there is a definite risk of sudden death with EDMD. A meta-analysis of 299 patients with LMNA gene mutation by van Berlo et al. showed that incidence of sudden death was 46% and it was much higher than incidence of death due to heart failure which was 12%. The mean age of sudden death was reported to be 46 years in that study [4]. In another study, the incidence of sudden death was found to be 41% (30 out of 73 cases) in X-linked EDMD. Only 4 patients among those had minor subjective symptoms like dizziness or syncopal episodes and the rest were symptom free. The age of sudden death in that population ranged from 25 to 59 years and 26 died before the age of 50 years [5]. Sudden death has also been reported in a female carrier of X-linked EDMD at the age of 45 years. In this patient, the 2D echocardiogram and doppler study were normal prior to death suggesting malignant arrhythmia secondary to EDMD as a possible cause of death [15].

Conduction block is considered the major cause of sudden death, as autopsy of sudden death cases showed significant atrial dilation and loss of atrial myocardium with fibro adipose tissue replacement [15,16]. Based on this and the fact that the progression of cardiac dysfunction is unpredictable, permanent pacemaker implantation in EDMD with any degree of AV block with or without symptoms is considered a class IIb (level of evidence C) indication [17].

However, there is a growing body of evidence indicating ventricular arrhythmias as a cause of sudden death in EDMD. In the meta-analysis by van Berlo et al., 50% sudden deaths occurred in those who had pacemaker versus 43% sudden deaths in those who did not have a pacemaker indicating that a pacemaker did not protect against sudden death. In the same study, of the 23 patients who died suddenly before the age of 60, 10 (43%) had a pacemaker, suggesting a pacemaker does not prolong life [4]. Fernandez et al. reported a sudden cardiac death in a 28 year old male with lamin A/C gene mutation who had mild left ventricular enlargement, an ejection fraction greater than 50%, normal 12 lead ECG, and a normal Holter-ECG [18]. Nigro et al. reported the first case of ICD implantation for primary prevention of sudden death in a 13 year old X-linked EDMD male patient with normal ejection fraction [19]. In another case Golzio et al. reported an autosomal dominant EDMD female with ejection fraction of 40% who received three appropriate ICD shocks for three episodes of fast polymorphic ventricular tachycardia rapidly deteriorating into ventricular fibrillation, thus preventing sudden death [20]. In a prospective study, Meune et al. subjected 19 EDMD patients with LMNA gene mutation to prophylactic ICD implantation. The mean ejection fraction was 58% in this study group. Over a period of 5 year follow up, 6 patients received shock for ventricular fibrillation, two patients received shocks for ventricular tachycardia, and one received anti-tachycardia pacing for ventricular tachycardia [21]. Sanna et al. prospectively studied 10 consecutive EDMD patients with lamin A/C gene mutations. They reported one sudden death in a 48 year old male with ejection fraction 56%. They also found non sustained ventricular tachycardia in 5 patients over a period of 29 months follow up, 2 of whom had normal ejection fraction [22]. These studies prove that fatal ventricular tachyarrhythmia can occur in the absence of significantly compromised left ventricular systolic function and pacemaker implantation alone does not prevent sudden death.

There are no clear predictors of sudden death in EDMD patients. Ventricular tachyarrhythmias are thought to occur secondary to fibrosis in the ventricles [23]. A recent study showed that EDMD patients without compromised ejection fraction had abnormal left ventricular function in terms of lower early diastolic myocardial velocity gradients and significant reduction in inferior wall contractility (measured by cardiovascular magnetic resonance strain). Interestingly, there was no fibrosis detected by magnetic resonance in these patients which might indicate that fatal ventricular arrhythmias might not be due to fibrosis and scarring alone [24]. However, the temporal relation between these abnormal ventricular function and sudden death is unknown. Although serum markers like tenasin-C levels and auto antibodies to troponin I have been found in EDMD, there was no significant correlation between the levels, cardiac symptomatology and echocardiographic findings [25,26]. Blood glutathione levels were recently shown to decrease in patients with lamin A/C gene mutation. All the patients in that study had ejection fraction of greater than 40%. Blood glutathione level positively correlated with both left and right ventricular contractility. The decrease in levels in LMNA mutated subjects was related to the degree of cardiac involvement rather than to phenotypic differences [27]. Again, this study did not look at end point of sudden death, and hence it is unknown if decrease in blood glutathione can be served as a marker to predict sudden death.

Currently there is no treatment available for EDMD although there is hope for definitive drug therapy in future. Inhibition of extracellular signal-regulated kinase (ERK) with PD98059 has shown to prevent cardiomyopathy in both X-linked and autosomal dominant EDMD in mice model [28,29]. No such studies with PD98059 have been done in humans. Management strategies in EDMD include physiotherapy,orthoses and surgery, preservation of respiratory function, pacemaker implantation for cardiac conduction abnormalities, and a regular follow up with a cardiologist. Anticoagulation in patients with atrial fibrillation, atrial flutter or standstill has been recommended by Boriani et al., but is not a part of guidelines [12]. An ICD is not currently recommended for EDMD patients who do not have cardiomyopathy. Table 1 shows current indications of an ICD [17]. Our case and a review of the literature till date indicate that an ICD can prevent sudden death in EDMD patients. An ICD was definitely life saving for our patient. Had the VT not been terminated by anti-tachycardia pacing, he would have got an ICD shock. If only pacemaker was implanted, the VT could have been fatal for our patient.
Table 1: Indications for an ICD.

| Class I | Level of evidence A | 1) Survivors of cardiac arrest due to ventricular fibrillation, or hemodynamically unstable ventricular tachycardia (VT) after evaluation to exclude any reversible causes.  
2) LVEF<35% due to prior myocardial infarction who are at least 40 days post myocardial infarction and are in NYHA functional class II or III.  
3) LVEF<30% due to prior myocardial infarction who are at least 40 days post myocardial infarction and are in NYHA functional class I. |
| Class IIa | Level of evidence B | 1) Structural heart disease and spontaneous VT irrespective of hemodynamic stability.  
2) Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or ventricular fibrillation at electrophysiological study.  
3) Nonischemic dilated cardiomyopathy with LVEF<35% that are in NYHA functional class II or III.  
4) Nonsustained VT due to prior myocardial infarction, LVEF less than or equal to 40%, and inducible ventricular fibrillation or sustained VT at electrophysiological study. |
| Class IIb | Level of evidence B | 1) Patients with long QT syndrome who are experiencing syncope and/or VT while on beta blocker.  
2) Sustained VT with normal or near normal ejection fraction.  
3) Hypertrophic cardiomyopathy that have one or more major risk factor for sudden cardiac death (SCD).  
4) Prevention of SCD in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy who have one or more risk factor for SCD.  
5) Nonhospitalized patients awaiting transplant.  
6) Patients with Brugada syndrome who have had syncope.  
7) Patients with Brugada syndrome who have documented VT that did not result in cardiac arrest.  
8) Patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blocker.  
9) Cardiac sarcoidosis, gaint cell myocarditis, or Chagas disease. |
| Class IIb | Level of evidence C | 1) Patients with no ischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional Class I.  
2) Patients with long-QT syndrome and risk factors for SCD.  
3) Patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause.  
4) Patients with a familial cardiomyopathy associated with sudden death. |

## Conclusion

To conclude, there is no relationship between the severity of cardiac and skeletal muscle involvement in EDMD. In our case, the patient presented with significant cardiac conduction abnormality without any major skeletal muscle involvement. Therefore, the clinicians should be vigilant about the diagnosis of EDMD, especially in the patients with strong family history of pacemaker implantation and sudden cardiac death who present with cardiac manifestations. Moreover, it is clear that sudden death is a major concern in EDMD and pacemaker implantation does not seem to prevent it. Also, an ICD implantation has clearly shown to prevent sudden deaths in EDMD. Given the lack of clear predictors of sudden death and the mortality benefit of an ICD, it would be prudent to implant an ICD rather than a pacemaker in EDMD patients.

## References


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