ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–8
https://doi.org/10.1093/ehjcr/ytad013

CASE SERIES
Electrophysiology

Cardiac manifestations and clinical management of X-linked Emery-Dreifuss muscular dystrophy: a case series

Niharika Kashyap[1,2], Anish Nikhanj [1,2], Luke R. Gagnon[1,2], Basel Moukaskas[1,2], Zaeem A. Siddiqi[3], and Gavin Y. Oudit [1,2]*

[1]Division of Cardiology, Department of Medicine, University of Alberta, 8440 112 Street NW, Edmonton, Alberta T6G 2R7, Canada; [2]Mazankowski Alberta Heart Institute, University of Alberta, 11220 83 Avenue NW, Edmonton, Alberta T6G 2J2, Canada; and [3]Division of Neurology, Department of Medicine, University of Alberta, 8440 112 Street NW, Edmonton, Alberta T6G 2R7, Canada

Received 24 January 2022; first decision 30 December 2022; accepted 9 January 2023; online publish-ahead-of-print 11 January 2023

Background Heart disease is an under-recognized cause of morbidity and mortality in patients with Emery-Dreifuss muscular dystrophy (EDMD). Arrhythmias and conduction delays are highly prevalent and given the rarity of this disease the patient care process remains poorly defined.

Case summary This study closely followed four adult patients from the Neuromuscular Multidisciplinary Clinic (Alberta, Canada) that presented with X-linked recessive EDMD. Patients were assessed and managed on a case-by-case basis. Clinical status and cardiac function were assessed through clinical history, physical examination, and investigations (12-lead electrocardiogram, 24 hour Holter monitor, transthoracic echocardiogram, and plasma biomarkers). Conduction disease, requiring permanent pacemaker, was prevalent in all patients. With appropriate medical therapy over a median follow-up period five years the cardiac status was shown to have stabilized in all these patients.

Discussion We demonstrate the presentation of arrhythmias, conduction abnormalities, and chamber dilation in adult patients with X-linked EDMD. Cardiac medications and pacemaker therapy are shown to prevent adverse outcomes from these complications. Patients with EDMD are expected to develop heart disease early and prior to the development of an overt neuromuscular phenotype. These patients should be closely monitored in a multidisciplinary setting for effective management to improve their clinical outcomes.

Keywords Emery-Dreifuss muscular dystrophy • Arrhythmias • Dilated cardiomyopathy • Pacemaker • Case series

ESC Curriculum 2.2 Echocardiography • 5.3 Atrial fibrillation • 5.9 Pacemakers • 5.10 Implantable cardioverter defibrillators • 6.5 Cardiomyopathy

Learning points

- X-linked Emery-Dreifuss muscular dystrophy (EDMD) is a rare neuromuscular disease in which the assessment and management of patients is poorly defined.
- Heart disease in EDMD is characterized by atrial and ventricular tachyarrhythmias, atrial standstill, conduction abnormalities and chamber dilation.
- Multidisciplinary approach to management of heart disease and comorbidities is critical in these vulnerable patients to prevent progression and sudden cardiac risk.

* Corresponding author. Tel: +780 407 8569, Fax: +780 407 6452, Email: gavin.oudit@ualberta.ca
Handling Editor: Giulia Ferrannini
Peer-reviewers: Bruno Rocha; Brian Halliday
Compliance Editor: Lavanya Athithan
Supplementary Material Editor: Jonathan Senior

Introduction

X-linked recessive (XLR) Emery-Dreifuss muscular dystrophy (EDMD) is the most common EDMD subtype caused by reduced or loss-of-function in the nuclear membrane protein emerin.[1–3] Emerin is associated with gene regulation, stabilization of the nuclear membrane, and plays a role in intercalated disc function in cardiomyocytes.[4,5] The classic phenotypic EDMD presentation is characterized with early joint contractures, slow progressive muscle wasting and weakness, and cardiac conduction abnormalities.[2] Skeletal muscle involvement typically precedes cardiac involvement.[6] Due to the slow progression of the disease, symptoms are often undetected, allowing for the progression of serious cardiac abnormalities and increased risk of sudden cardiac risk (SCD).[4] There are currently no disease-specific therapies for EDMD therefore management and therapeutic strategies are patient specific. Heart disease, clinical management, and outcomes in *EMD*-associated XLR-EDMD is poorly defined compared with *LMNA*-associated autosomal dominant (AD) EDMD.[7] This case series assesses the disease progression, therapeutic management, and outcomes of four patients with *EMD*-associated XLR-EDMD in a multidisciplinary setting.[8]

Timeline of clinical progression in four patients with Emery-Dreifuss muscular dystrophy

	Patient 1
23 year	Genetically confirmed for EDMD
27 year	Single-chamber pacemaker implantation
36 year	NMMD Clinic Enrolment
36 years–44 years	Advanced AV block and permanent atrial fibrillation. Prolonged QRS duration and QTc interval on 12-lead electrocardiogram.
	Patient 2
20 year	Genetically confirmed for EDMD
31 year	Dual chamber pacemaker implantation
39 year	NMMD Clinic Enrolment
31 years–40 years	Nodal dysfunction treated with pacemaker. Marginal thinning of the myocardium and systolic dysfunction. Managed dyslipidemia with cholesterol-lowering drugs.
	Patient 3
20 year	Genetically confirmed for EDMD
21 year	Single-chamber pacemaker implantation
50 year	NMMD Clinic Enrolment
43 years–50 years	Normal left ventricular dimensions with increased ventricular mass. History with permanent atrial fibrillation. History of sleep disordered breathing, and mild pulmonary hypertension.
50 year	Elevated blood pressure, dilated ventricles and elevated ventricular mass is treated with increased dose of perindopril and discontinued modafinil. Improved ventricular dimensions and mass.
51 years–55 years	Advancing atrial myopathy with increased QRS duration is treated with switch to apixaban.
	Patient 4
6 year	Genetically confirmed for EDMD
14 year	Single-chamber pacemaker insertion and intraatrial re-entrant tachycardia (IART) ablation for AV block and atrial tachycardia.
18 year	NMMD Clinic Enrolment
18 year	IART ablation and subcutaneous implantable cardioverter-defibrillator. Started on perindopril.
14 years–20 years	Normal ventricular structure and function.

Patient 1

A thirty-seven-year-old male XLR-EDMD patient was referred to the NMMD clinic (*Figure 1A*). The patient exhibited symptoms of mild joint contractures and generalized weakness that required the use of a cane to ambulate independently (*Table 1*). From a cardiac perspective, the patient had a history of advanced AV block and permanent atrial fibrillation (AF), for which he had a pacemaker implanted 10 years prior to enrolment. In addition to the patient's pacemaker, he was taking bisoprolol 7.5 mg q.d. for rate control of the underlying permanent AF and enteric-coated acetylsalicylic acid (ECASA) for thromboembolism prophylaxis prevention.

Physical examination demonstrated a regular heart rate of 70 bpm and blood pressure of 102/68 mmHg (*Table 1*). Baseline B-type natriuretic peptide (BNP) and troponin I (TnI), were normal at 23.0 pg/mL and 0.1 ng/mL, respectively.[9] Creatine kinase (CK) was mildly elevated at 345 U/L indicating active muscle damage and inflammation.

The 12-lead electrocardiogram (ECG) recorded AF, which was ventricularly paced by a single-chamber pacemaker (*Figure 2A*). ECG parameters included a prolonged QRS duration of 148 ms and a QTc interval of 452 ms (*Table 1*). At 4-years and 6-years follow-up, ECG parameters performed were relatively unchanged.

Baseline TTE data showed normal cardiac structure, with no signs of dilation or hypertrophy with left ventricular mass index (LVMI) at 57 g/m^2, low-normal function with a left ventricular (LV) ejection fraction (EF) at 55%, left atrial volume index (LAVI) of 12 mL/m^2, and no signs of valvular disease (*Table 1*). Echocardiogram was performed at 4-year and 8-year follow-up demonstrating stable cardiac function with minimal changes to the cardiac structure (*Figure 3B*). Over the course of 8 years, LV dimensions remained normal with a marginal increase in left ventricular end diastole diameter (LVIDd) from 39 to 45 mm and left ventricular end systole diameter (LVIDs) from 29 to 30 mm. There was a marginal increase in LVMI at 49 g/m^2 to 66 g/m^2. Qualitative assessment of atria size remained normal. In addition, LVEF remained stable from 55 to 60% and LAVI increased from 12 mL/m^2 to 29 mL/m^2 (*Figure 3B*). Overall, the patient is predominantly affected by severe conduction deficits that are monitored through periodic assessment at the NMMD clinic and managed with the use of device therapy and medications.

Patient 2

A thirty-nine-year-old male XLR-EDMD patient, the brother of Patient 1, was referred to the NMMD clinic presented with advanced symptoms

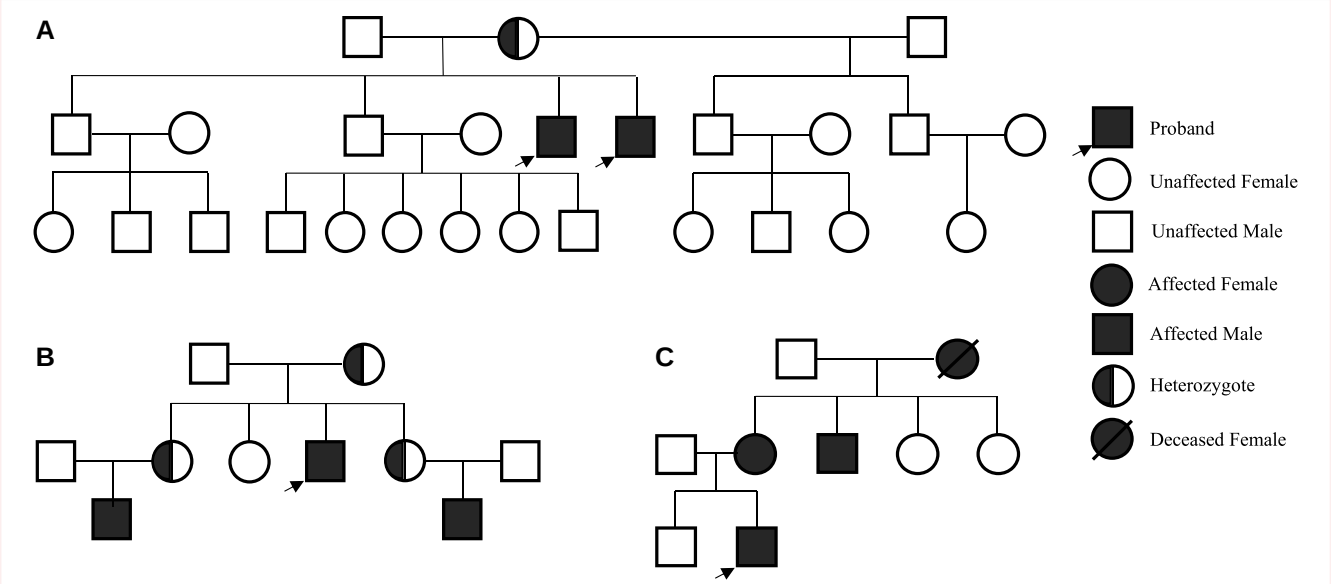

Figure 1 Pedigree chart depicting family history of *EMD* gene-associated in an X-linked recessive mode of inheritance in (*A*) proband 1 and 2, (*B*) proband 3, and (*C*) proband 4. Proband 3 refused to share family history regarding his children.

including elbow contractures and weak ankles requiring a cane for balance and ambulation (*Figure 1A*). In terms of comorbidities, the patient has a history of sleep disordered breathing (SDOB) for which continuous positive airway pressure (CPAP) was prescribed (but not used on a regular basis due to patient discomfort), and dyslipidemia that was treated with rosuvastatin 5 mg q.d. and maintained his low-density lipoprotein at 3.0 mmol/L (*Table 1*). From a cardiac perspective, the patient had a history of heart failure, syncope, and sinoatrial (SA) and AV nodal dysfunction, for which a dual chamber pacemaker was inserted 8 years prior to clinic enrolment (a generator change was performed seventeen years after insertion) (*Table 1*).

Upon physical examination, the patient was bradycardic with a heart rate of 57 bpm and hypertensive with a blood pressure of 159/93 mmHg; however, no prior history of hypertension was noted, and no additional cardiovascular signs and symptoms were reported (*Table 1*). CK levels were elevated at 434 U/L.

Baseline ECG study showed sinus rhythm with a QRS duration of 102 ms and a prolonged QTc interval of 452 ms (*Table 1*). An 8-year follow-up ECG showed the QRS duration remained normal and unchanged and QTc interval incrementally decreased to 437–403 ms (*Figure 3B*).

Baseline TTE data showed normal cardiac structure, with no evidence of dilation (LVIDd = 46 mm; LVIDs = 28 mm) or hypertrophy (LVMI = 80 g/m^2), normal systolic function (LVEF = 62%), and no signs of valvular heart disease (*Table 1*). Follow-up TTE 2-years and 3-years later demonstrated LV dimensions remained normal (LVIDd = 46 and 51 mm; LVIDs = 29 and 32 mm) and normal to borderline normal systolic function (LVEF = 61% and 52%) with no signs of hypertrophy (LVMI = 49 g/m^2 and 58 g/m^2) (*Figure 3B*). From baseline, LV mass index in this patient reduced from 80 g/m^2 to 58 g/m^2 (*Figure 3B*). Left atrial volume (LAVI = 22 mL/m^2 and 25 mL/m^2) remained stable and normal (*Figure 3B*). Qualitative assessment of atrial size showed the right atria was initially mild to moderately enlarged that recovered to normal size and the left atria size remained normal and stable. Overall, ECG and TTE parameters remained within the normal range; however, there was marginal thinning of the myocardium and decreased systolic function.

Patient 3

A fifty-year-old male XLR-EDMD patient was referred to the NMMD clinic and presented with hand weakness and wrist contractures (*Figure 1B*). The patient had a history of smoking and SDOB for which CPAP was used with good compliance and was taking modafinil for daytime sleepiness. He has a history of mild pulmonary hypertension with non-invasive right ventricular systolic pulmonary arterial pressure of 35–40 mmHg. The patient had AF that he received a single-chamber pacemaker 29 years prior, which progressed to permanent AF (*Table 1*). Due to the uncertain risk of thromboembolic events from permanent AF, patient was prescribed ECASA 81 mg q.d.

On examination, he was hypertensive and bradycardic with a heart rate of 50 bpm and blood pressure of 145/90 mmHg. Plasma BNP and TnI were within normal ranges, and CK was elevated at 1695 U/L. Baseline Holter monitor confirmed AF with AV conducted beats and regular junctional tachyarrhythmias.

Baseline ECG study showed AF and ventricular-paced complexes with QRS duration of 102 ms, and QTc interval of 417 ms. At 6-year follow-up, his blood pressure was elevated to 172/94 mmHg; therefore his perindopril was uptitrated from 2 mg q.d. to 4 mg q.d., and modafinil was discontinued. After medication adjustments, follow-up ECG 1-year and 3-years later showed QRS duration increased from 156 to 160 ms over 4-year time span (*Figure 3B*). Given his advancing age and progression of atrial myopathy, patient was switched from ECASA to using a direct oral anticoagulant (apixaban 5 mg twice daily).

Baseline TTE demonstrated mild aortic dilation, moderate mitral and tricuspid regurgitation, mild right ventricular (RV) dilation (RVd basal = 5.4 cm) and severely dilated left and right atria, which did not change during follow-up assessments. Patient exhibited mildly reduced LVEF of 51% as well as normal LV dimensions (LVIDd = 55 mm) and elevated ventricular mass (LVMI = 124 g/m^2) (*Table 1*). Echocardiogram showed significant improvements before and after medication adjustments with reduced LV dimensions (LVIDd = 62 and 58 mm; LVIDs = 35 and 25 mm), and improved hypertrophy (LVMI = 182 g/m^2 and 135 g/m^2) (*Figure 3B*). Systolic function remained steady ranging from 50–55% over the 4-year-period (*Figure 3B*). In addition, LAVI increased from

Table 1 Clinical characteristics of patients with Emery-Dreifuss muscular dystrophy

Patient	Age(y)/ sex/BMI (kg/m^2)	Neuromuscular symptoms	Cardiovascular risk factors	Cardiac abnormalities	HR (bpm)/ sBP (mmHg)/ dBP (mmHg)	Baseline ECG findings (ms)	Baseline TTE findings	Baseline medications and dose (mg)	Cardiac intervention and devices	Chamber and percent pacing
1	36/M/13.6	Elbow and wrist, contractures, Generalized weakness (cane)	None	Permanent AF	64/102/68	QRS: 148 QTc: 452, AF, ventricular-paced	LVEF: 55% LVMI: 57 g/m^2 LVIDd: 40 mm LVIDs: 29 mm LAVI: 12 mL/m^2	Bisoprolol 7.5 mg ECASA 81 mg	Baseline: Single-chamber pacemaker	RV: 99.5%
2	39/M/25.7	Elbow contractures, Generalized weakness	SDOB (CPAP), dyslipidemia	SA & AV node dysfunction	57/159/93	PR: 140 QRS: 102 QTc: 452, Multiple PACs	LVEF: 62% LVMI: 80 g/m^2 LVIDd: 46 mm LVIDs: 28 mm LAVI: 23 mL/m^2	Rosuvastatin 10 mg	Baseline: Dual chamber pacemaker	RA: 94.5% RV: 2.0%
3	50/M/28.1	Hand weakness Wrist, contractures	Smoker, SDOB (CPAP), hypertension	Permanent AF, severe LVH, Mild RV dilation, Mild mitral & aortic valve regurgitation	55/145/90	QRS: 102 QTc: 417 AF	LVEF: 50% LVMI: 124 g/m^2 LVIDd: 55 mm LVIDs: 31 mm LAVI: 39 mL/m^2	Perindopril 2 mg, ECASA 81 mg, Modafinil	Baseline: Single-chamber pacemaker Follow-up: Perindopril 4 mg, discontinued Modafinil, Switched ECASA to Apixaban.	RV: 48.5%
4	18/M/28.1	Scoliosis, leg weakness	None	SA node dysfunction VT, Atrial flutter, Mild RV dilation	51/144/43	QRS: 94 QTc: 443, Junctional escape rhythm	LVEF: 64% LVMI: 86 g/m^2 LVIDd: 52 mm LVIDs: 29 mm LAVI: 24 mL/m^2	ECASA 81 mg	Baseline: IART ablation, single-chamber pacemaker, Follow-up: Perindopril 2 mg Implanted Subcutaneous ICD	RV: 4.6%

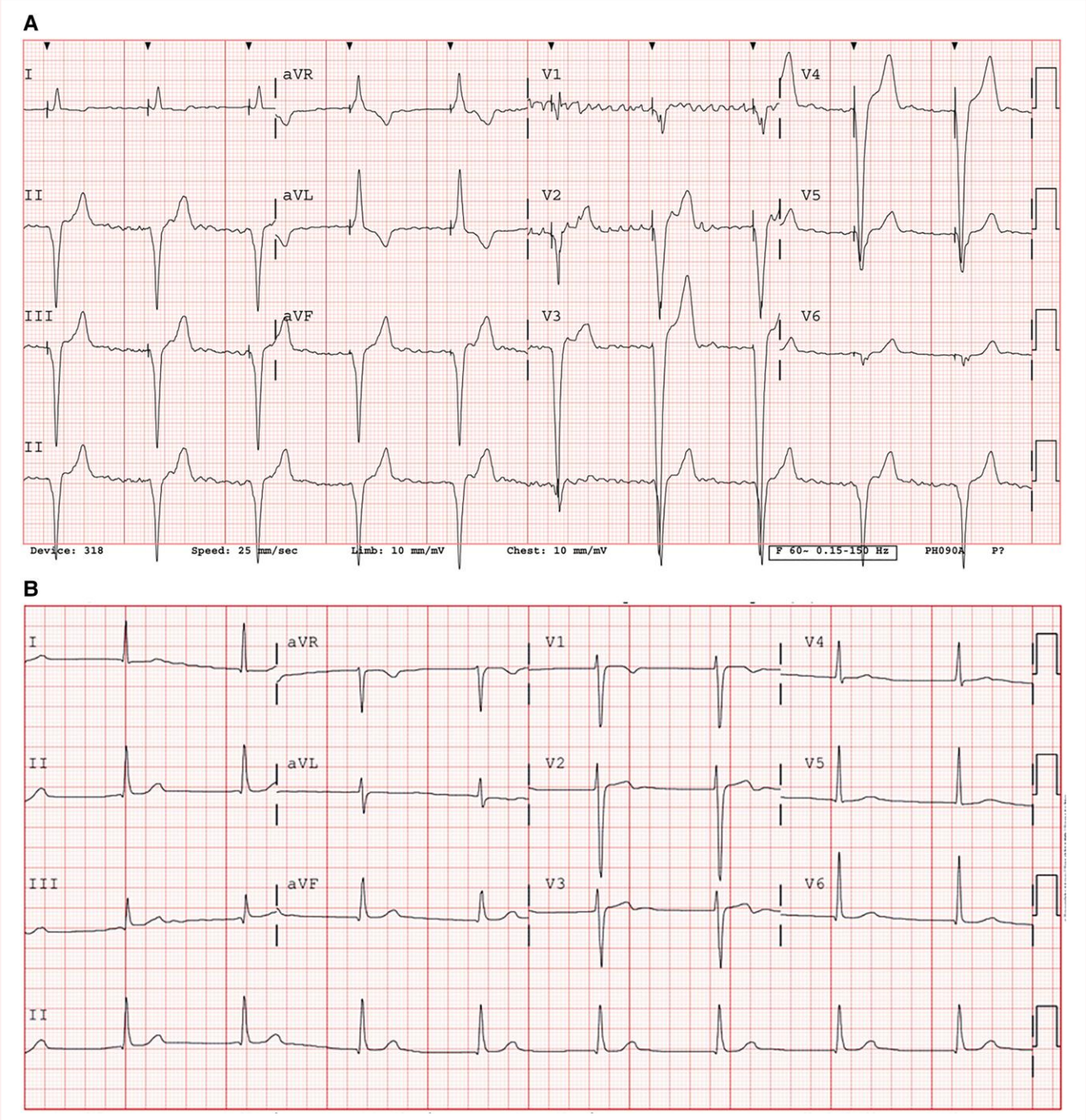

Figure 2 Electrocardiograms from (*A*) patient 1 depicting atrial fibrillation with ventricular-paced rhythm at 60 bpm, and (*B*) Patient 4 depicting junction escape rhythm at the rate of 50 bpm with normal axis and no hypertrophy.

63 mL/m^2 to 112 mL/m^2 (*Figure 3B*). Overall, LV structure and function improved over the 4-year-period following discontinuation of modafinil and uptitration of perindopril.

Patient 4

An 18-year-old male XLR-EDMD patient referred to the NMMD Clinic presenting with leg and ankle weakness, scoliosis, and a history of falls (*Figure 1C*). The patient experienced progressive cardiac involvement with hypertension, recurrent atrial tachycardia, SA and AV node dysfunction, and history of non-sustained VT.

Upon enrolment, the patient was bradycardic with a heart rate of 51 bpm and elevated blood pressure of 144/43 mmHg, while prescribed ECASA 81 mg for thromboembolism prophylaxis prevention due to possible increased risk related to atrial abnormalities including atrial standstill.

Pre-device ECG showed a junctional escape rhythm with normal QRS duration of 94 ms, and a prolonged QTc interval of 443 ms (*Figure 2B*). The patient received a single-chamber pacemaker for AV

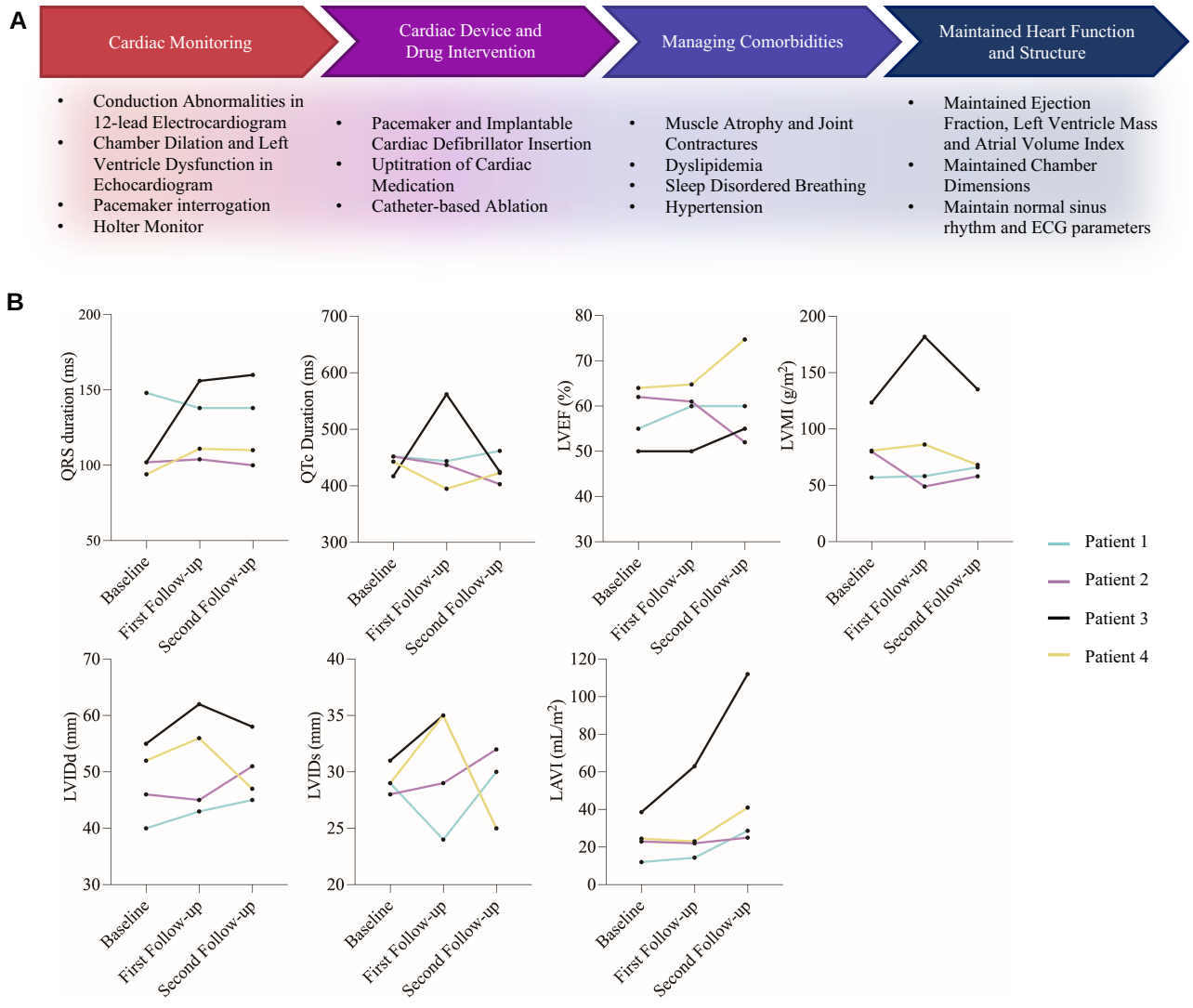

Figure 3 (*A*) Cardiac monitoring and management strategies for X-linked EDMD patients (*B*) illustrated by 12-lead electrocardiogram (QRS duration, qtc interval) and echocardiogram (LVEF, LVIDd, LVIDs, LVMI, LAVI) parameters in patients 1–4 to track disease progression from baseline to median 3-year first follow-up and 5-year second follow-up.

block. Follow-up monitoring revealed episodes of atrial tachycardia requiring intraatrial re-entrant tachycardia (IART) ablation. Four years later, a subcutaneous ICD for primary prevention of SCD was inserted due to the potential risk of developing VT given several prior episodes of non-sustain VT. Alternatively, the patient could have been upgraded to a transvenous ICD system. In addition to device therapy, the patient was started on perindopril 2 mg.

Baseline TTE showed normal LV dimensions (LVIDd = 52 mm; LVIDs = 29 mm) and normal systolic function at 64%. Patient exhibited mild mitral, tricuspid, and pulmonary valve regurgitation, which progressed to moderate tricuspid regurgitation. Follow-up TTE was performed 2-years and 6-years following pacemaker implantation showed a moderately enlarged right atrium and mildly enlarged left atrium (*Table 1*). Ventricular dimension remained stable (LVIDd = 56–47 mm; LVIDs = 35–25 mm), and systolic function remained preserved within normal limits (LVEF = 60–70%) (*Figure 3B*). Overall, LV structure and function remained stable, but the main concern was recurrent atrial tachycardia and nodal dysfunction.

Discussion

We report four cases of XLR-EDMD and a longitudinal assessment of their clinical profile, cardiac outcomes and the therapeutic strategies utilized in clinical management. We discuss the variation in cardiac involvement and evolution of cardiac monitoring parameters over time. Clinical cardiac monitoring for EDMD patients consists of ECG, Holter monitoring, laboratory markers and TTE to monitor conduction abnormalities, arrhythmias, and changes in heart structure and function (*Figure 3A*).[10,11]

Conduction abnormalities and arrhythmias are the predominant cardiac manifestation in EDMD, presenting as bradycardia, prolonged PR interval, or reduced *P* wave amplitude on ECG. The incidence of conduction abnormalities and arrhythmias increase with age and include atrioventricular (AV) conduction delays, and atrial and ventricular arrythmias.[12] In XLR-EDMD patients, age of onset for AVB is earlier, and there is a high occurrence of AF/atrial flutter compared with AD-EDMD.[6,7] In addition, atrial standstill is the primary cause of cardiac death in XLR-EDMD that could be averted with pacemaker

implantation.[6,13] Two patients developed permanent AF, for whom underwent device intervention in the third decade of their life. The other two patients exhibit nodal dysfunction, for whom underwent device intervention in the second decade of their life. All the patients received pacemaker therapy at the first indications of bradycardia, sinus node dysfunction, or as preventative measure. Indeed, due to the prevalence of atrial standstill in EDMD, European Society of Cardiology guidelines recommend pacing device intervention at first indication of conduction disturbances or bradyarrhythmias, or before the age of 30.[14]

Sudden cardiac death and ventricular arrhythmias are associated with AD-EDMD, thus early ICD intervention should be considered along with pacemaker implantation.[7] Despite the rarity of VT in XLR-EDMD, Patient 4 had several episodes of non-sustain VT, which emphasizes the importance of consistent follow-up with Holter and cardiac device monitoring. Subsequently, this patient received a subcutaneous ICD as primary prevention of SCD and VT. Cardiac magnetic resonance studies suggest a relationship between remodelling in areas associated with the conduction system to atrial conduction abnormalities and risk of SCD.[15]

Our study is one of few to describe successful atrial ablation procedure in EDMD patients. Patient 4 was diagnosed with recurrent atrial tachycardia detected on a routine ECG and Holter study (*Figure 3A*). Previous case studies have described success with atrial ablation procedure in paediatric and young adult EDMD patients, in which patients present with various types of supraventricular arrhythmias.[16,17] Butt *et al.* demonstrated a successful approach to atrial ablation using 3D mapping on a 21-year-old male EDMD patient presenting with sustained VT and atrial flutter.[17] Unsuccessful ablation have been linked to adverse outcomes including systolic dysfunction, embolic stroke, and heart transplant in this cohort.[16,18,19]

There is a high prevalence of disabling embolic stroke in EDMD patients untreated with anticoagulation or aspirin treatment.[16,20,21] Current guidelines for heart failure cohorts have not been validated in EDMD management nor are they tailored to patients with rare diseases. The CHADSVasc score for AF stroke risk has not been validated in the EDMD population and the use of anticoagulation and antiplatelet therapy in EDMD patients is controversial.[20] Our approach to therapeutics was based on atrial abnormalities and a potential increased risk of thromboembolic events and strokes; we used low-dose ECASA as a preventative measure for patients 1, 3, and 4, as per clinician and patient preference although not evidence-based. In addition, anticoagulation therapy may be preferred treatment option depending on age and severity of atrial myopathy as seen in patient 3. The ideal approach to thromboprophylaxis strategy has not been established, thus further research is needed to assess prophylactic efficacy of anticoagulation therapy.[20]

Muscle weakness and upper limb contractures were the most prevalent neuromuscular symptoms in our cohort. Each case exhibited some degree of skeletal muscle involvement that did not correlate with severity of heart disease. Of the three patients to receive biomarker assessment, all exhibit elevated levels of CK consistent with EDMD-induced scapulohumeroperoneal muscle wasting.[1] In EDMD patients, CK levels can range from normal to 15 times the upper limit, and there is no direct link between CK levels and cardiac or skeletal muscle involvement.[4] In addition, cardiac biomarkers, BNP and TnI, were at normal levels in two patients thereby limiting the use of these cardiac biomarkers in these patients.[9] Marchel *et al.* have shown elevated BNP as a predictor of mortality in EDMD patients.[22]

In addition to laboratory markers, our patients were assessed by TTE for cardiac structure and function at baseline and median follow-ups of 3-years and 5-years at the Level III echocardiography laboratory (*Figure 3A*). Systolic function remained preserved with LVEF above 50% for all four patients across all timepoints. Compared with XLR-EDMD, systolic dysfunction is more prevalent in AD-EDMD.[23] EDMD is characterized by a high prevalence of dilated atria and LV.[24] Three patients exhibit dilated atria, and two patients exhibit dilated LV. Dilated cardiomyopathy is rare in XLR-EDMD compared with other X-linked dystrophies; however, AD-EDMD is associated with ventricular dilation.[25] Overall, LV dimensions remained relatively stable over time for three of the four patients, which may be influenced by several factors including the short follow-up, use of medical therapies, and patient lifestyle choices. Patient 3 was the only patient of our cohort to develop eccentric hypertrophy that improved after discontinuation of modafinil and uptitration of perindopril. Modafinil is not recommended in patients with hypertrophy and can induce/worsen hypertension, thus we suspect that the worsening of blood pressure, hypertrophy, and dimensions in Patient 3 were associated with the sympathomimetic effects of modafinil. We cannot say whether the improvements were directly linked to modafinil discontinuation or improved control of hypertension, but likely a combination of the two changes.

Family genetic counselling is imperative for diagnosis and early intervention for both AD-EDMD and XLR-EDMD to prevent disease progression. In addition to early intervention and annual monitoring, cardiac devices and pharmacotherapy are foundational aspects of our therapeutic strategy to treat conduction abnormalities and prevent further complications (*Figure 3A*).[7] Several factors may influence our patient outcomes including early pacemaker implantation prior to enrolment at our clinic, the use of CPAP therapy, and extent of conduction abnormalities in our cohort. Thus, cardiac care in a multidisciplinary setting serve an important role in the management of this disease.[8,9,26,27] The recognition and management of SDOB in patients with EDMD is important since nocturnal hypoxia and hypercapnia secondary to hypoventilation can affect the cardiovascular system and lead to poor outcomes.[28,29] Monitoring cardiac comorbidities, such as, hypertension, SDOB, and dyslipidaemia is an important aspect of our therapeutic approach, thus strict management with statin therapy, positive airway pressure therapy and renin–angiotensin system blockade prevent further complications. Considering the extent of neuromuscular, cardiovascular, and other comorbidities experienced by the muscular dystrophies, these patients benefit from a multidisciplinary approach to their care management.[8,9,26,27,30]

Patient perspective

Variability in cardiac manifestations pose a challenge to the clinical management of EDMD patients. Conduction system disease and dilated atria are the two most prevalent cardiac manifestations seen in patients with EDMD. Early indications of conduction disease include bradycardia and prolonged PR interval. Underlying conduction disease should be an indication for pacemaker insertion at the first sign of bradycardia or nodal dysfunction. Regular monitoring with device interrogation, ECG and TTE allow for close monitoring of disease progression.

Lead author biography

Niharika Kashyap is currently an MSc candidate in the Faculty of Medicine and Dentistry at the University of Alberta in Canada. She graduated from the University of Western Ontario with a Bachelor of Medical Science in 2020. Her research is focused on the diagnostic and prognostic determinants of heart disease in patients with rare hereditary diseases, including muscular dystrophies.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Acknowledgements

We would like to acknowledge the patients, their families, and caregivers for their willing participation in this study.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as *Supplementary data*.

Consent: The authors confirm that informed and written consent for the publication of the case series was obtained from patients in line with COPE guidelines.

Conflict of interest: None declared.

Funding: This work was supported by the Motyl Graduate Studentship to A.N. in Cardiac Sciences from the University of Alberta.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Buckley AE, Dean J, Mahy IR. Cardiac involvement in emery dreifuss muscular dystrophy: a case series. *Heart* 1999;**82**:105–108.
2. Bialer MG, McDaniel NL, Kelly TE. Progression of cardiac disease in emery-dreifuss muscular dystrophy. *Clin Cardiol* 1991;**14**:411–416.
3. Manilal S. The emery-dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. *Hum Mol Genet* 1996;**5**:801–808.
4. Helbling-Leclerc A, Bonne G, Schwartz K. Emery-Dreifuss muscular dystrophy. *Eur J Hum Genet* 2002;**10**:157–161.
5. Wheeler MA, Warley A, Roberts RG, Ehler E, Ellis JA. Identification of an emerin-beta-catenin complex in the heart important for intercalated disc architecture and beta-catenin localisation. *Cell Mol Life Sci* 2010;**67**:781–796.
6. Marchel M, Madej-Pilarczyk A, Tymińska A, Steckiewicz R, Ostrowska E, Wysińska J, *et al.* Cardiac arrhythmias in muscular dystrophies associated with emerinopathy and laminopathy: a cohort study. *J Clin Med* 2021;**10**:732.
7. Wang S, Peng DQ. Cardiac involvement in emery-dreifuss muscular dystrophy and related management strategies. *Int Heart J* 2019;**60**:12–18.
8. Nikhanj A, Yogasundaram H, Miskew Nichols B, Richman-Eisenstat J, Phan C, Bakal JA, *et al.* Cardiac intervention improves heart disease and clinical outcomes in patients with muscular dystrophy in a multidisciplinary care setting. *J Am Heart Assoc* 2020;**9**:e014004. doi:10.1161/JAHA.119.014004.
9. Nikhanj A, Nichols BM, Wang K, Siddiqi ZA, Oudit GY. Evaluating the diagnostic and prognostic value of biomarkers for heart disease and Major adverse cardiac events in patients with muscular dystrophy. *Eur Heart J Qual Care Clin Outcomes* 2020;**7**:564–573.
10. Sanna T, Dello Russo A, Toniolo D, Vytopil M, Pelargonio G, De Martino G, *et al.* Cardiac features of emery-dreifuss muscular dystrophy caused by lamin A/C gene mutations. *Eur Heart J* 2003;**24**:2227–2236.
11. Nikhanj A, Yogasundaram H, Kimber S, Siddiqi ZA, Oudit GY. Clinical utility of 12-lead electrocardiogram in evaluating heart disease in patients with muscular dystrophy: assessment of left ventricular hypertrophy, conduction disease, and cardiomyopathy. *Ann Noninvasive Electrocardiol* 2021;**26**:e12876.
12. Groh WJ. Arrhythmias in the muscular dystrophies. *Heart Rhythm* 2012;**9**:1890–1895.
13. Sakata K, Shimizu M, Ino H, Yamaguchi M, Terai H, Fujino N, *et al.* High incidence of sudden cardiac death with conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. *Circulation* 2005;**111**:3352–3358.
14. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, *et al.* 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European society of cardiology (ESC). developed in collaboration with the European heart rhythm association. *Europace* 2013;**15**:1070–1118.
15. Blaszczyk E, Gröschel J, Schulz-Menger J. Role of CMR imaging in diagnostics and evaluation of cardiac involvement in muscle dystrophies. *Curr Heart Fail Rep* 2021;**18**:211–224.
16. Kovalchuk T, Yakovleva E, Fetisova S, Vershinina T, Lebedeva V, Lyubimtseva T, *et al.* Case reports: emery-dreifuss muscular dystrophy presenting as a heart rhythm disorders in children. *Front Cardiovasc Med* 2021;**8**:668231.
17. Butt K, Ambati S. Atrial arrhythmias in emery-dreifuss muscular dystrophy: approach to successful ablation. *HeartRhythm Case Rep* 2020;**6**:318–321.
18. Blagova O, Nedostup A, Shumakov D, Poptsov V, Shestak A, Zaklyasminskaya E. Dilated cardiomyopathy with severe arrhythmias in emery-dreifuss muscular dystrophy: from ablation to heart transplantation. *J Atr Fibrillation* 2016;**9**:1468.
19. Homma K, Nagata E, Hanano H, Uesugi T, Ohnuki Y, Matsuda S, *et al.* A young patient with emery-dreifuss muscular dystrophy treated with endovascular therapy for cardioembolic stroke: a case report. *Tokai J Exp Clin Med* 2018;**43**:103–105.
20. Boriani G, Gallina M, Merlini L, Bonne GL, Toniolo D, Amati S, *et al.* Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in emery-dreifuss muscular dystrophy. *Stroke* 2003;**34**:901–908.
21. Valenti AC, Albini A, Imberti JF, Vitolo M, Bonini N, Lattanzi G, *et al.* Clinical profile, arrhythmias, and adverse cardiac outcomes in emery-dreifuss muscular dystrophies: a systematic review of the literature. *Biology (Basel)* 2022;**11**:530.
22. Marchel M, Madej-Pilarczyk A, Steckiewicz R, Stolarz P, Peller M, Tyminska A, *et al.* Predictors of mortality and cardiovascular outcomes in emery-dreifuss muscular dystrophy in a long-term follow-up. *Kardiol Pol* 2021;**79**:1335–1342.
23. Marchel M, Madej-Pilarczyk A, Tymińska A, Steckiewicz R, Kochanowski J, Wysińska J, *et al.* Echocardiographic features of cardiomyopathy in emery-dreifuss muscular dystrophy. *Cardiol Res Pract* 2021;**2021**:1–7.
24. Arbustini E, Di Toro A, Giuliani L, Favalli V, Narula N, Grasso M. Cardiac phenotypes in hereditary muscle disorders: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;**72**:2485–2506.
25. Kułach A, Majewski M, Gąsior Z, Gardas R, Gościńska-Bis K, Gołba KS. Dilated cardiomyopathy with severe arrhythmias in emery-dreifuss muscular dystrophy. *Cardiol J* 2020;**27**:93–94.
26. Nikhanj A, Sivakumaran S, Yogasundaram H, Becher H, Kimber S, Siddiqi ZA, *et al.* Comparison of usefulness of cardiac resynchronization therapy in patients with type 1 myotonic dystrophy with versus without left bundle branch block. *Am J Cardiol* 2019;**124**:1770–1774.
27. Nikhanj A, Sivakumaran S, Miskew-Nichols B, Siddiqi ZA, Oudit GY. Ventricular tachycardia in patients with type 1 myotonic dystrophy: a case series. *Eur Heart J Case Rep* 2019;**3**:1–5.
28. Cowie MR, Linz D, Redline S, Somers VK, Simonds AK. Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:608–624.
29. Aboussouan LS. Sleep-disordered breathing in neuromuscular disease. *Am J Respir Crit Care Med* 2015;**191**:979–989.
30. Becane HM, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, *et al.* High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol* 2000;**23**:1661–1666.