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CASE REPORT
Other

Laminopathies: should Wenckebach be a cause for concern? A case report

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Background *LMNA* cardiomyopathy is a cause of dilated cardiomyopathy (DCM) characterized by aggressive heart failure, high risk of arrhythmias, and sudden cardiac death. We present a case of a male presenting with an *LMNA* mutation with an aggressive DCM leading to sudden cardiac death (SCD).

Case summary A 42-year-old male presented with the feeling of lethargy and intermittent dizziness. Electrocardiogram demonstrated atrioventricular block in keeping with Mobitz type 1, at a rate of 40 b.p.m. and cardiac monitoring showed non-sustained ventricular tachycardia. Cardiac magnetic resonance imaging showed preserved left ventricular (LV) ejection function (59%) but features suggesting DCM. These included mild LV dilatation with an end diastolic volume (EDV) of 213 mL and late enhancement showing a single mid myocardial focus of high signal over the distal right ventricular insertion point inferiorly and a linear area of high signal over the basal septum. After discussion at the cardiology multi-disciplinary meeting, a pacemaker was implanted so that beta-blockers could be initiated to suppress the ventricular arrhythmias. A laminopathy was suspected and if this was confirmed from genetic testing the plan was to upgrade to an implantable defibrillator. Due to stability, this was decided to be done in an outpatient setting. He unfortunately had an out-of-hospital VF arrest and died. Post-mortem showed subtle cardiomyopathy in keeping with a DCM. Genetic tests results were returned a few months later which confirmed a pathogenic variant in LMNA.

Discussion Because of the complexity of *LMNA*-related cardiac disease, they should be managed and followed up in centres with special expertise in inherited cardiomyopathy.

Keywords Laminopathy • Dilated cardiomyopathy • Familial • Ventricular fibrillation • Case report

Introduction

The nuclear proteins Lamin A and C are encoded by the *LMNA* gene. Mutations in the *LMNA* gene can cause a spectrum of diseases including certain types of muscular dystrophy, lipodystrophy, and cardiomyopathies.[1,2] In the heart, the spectrum is variable and can range from no apparent disease to isolated ventricular dilatation, arrhythmogenic cardiomyopathy, and dilated cardiomyopathy (DCM).[1,2] The penetrance of *LMNA* variants is extremely high by the age of 50 years and therefore can present with severe disease at a young age. We present a case of a young male presenting with an *LMNA* mutation with an aggressive DCM leading to sudden cardiac death (SCD).

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Learning points

- Cardiomyopathies are a subset of cardiac diseases which can cause significant morbidity and mortality and can include sudden cardiac death.
- The diagnosis of laminopathy should be considered in young patients presenting with Brady or tachyarrhythmias; seeing a variety of dysrhythmias in one individual is a key feature of laminopathies.
- There is unfortunately a high risk of sudden cardiac death even in early disease.
- The current recommendation is that implantable cardiac defibrillators are considered for patients with a confirmed genetic diagnosis who require pacing or have risk factors for sudden cardiac death.
- Deciding the immediate treatment for patients with features suggestive of laminopathy but without a confirmed genetic diagnosis is very challenging. In this cohort of patients for whom genetics is not yet available, multi-disciplinary discussions are essential to weigh up the pros and cons of implantation on an individual basis.

Timeline

Day 1	**Admission to hospital with lethargy and Electrocardiogram showing atrioventricular block with a Mobitz type I (Wenckebach) pattern with a heart rate of 40 b.p.m.**
Day 2	Transthoracic echocardiogram showed normal left ventricular (LV) systolic function with ejection fraction (EF) of 55–65% but dilated atria. Overnight cardiac monitoring revealed multiple episodes of non-sustained ventricular tachycardia.
Day 3	Cardiac magnetic resonance imaging showed preserved LV systolic function with an EF of 59%, and findings consistent with a dilated cardiomyopathy.
Day 4	Discussion in local and regional multi-disciplinary meetings. Decision made to perform genetic testing, a cardiomyopathy screen, and to implant a dual-chamber pacemaker so that beta-blockers could be initiated to suppress the ventricular arrhythmias. Outpatient plan to upgrade to an implantable cardioverter-defibrillator if a malignant genetic profile is identified.
Day 5	Dual-chamber pacemaker implanted, and beta-blockers initiated
Day 6	Discharged home with plan to be reviewed in outpatient cardiology and genetics clinic.
3 months after admission	Reviewed in cardiology clinic where pacing check showed episodes of atrial fibrillation and ventricular ectopics. Beta-blockers up-titrated to suppress the ectopics. Also advised to avoid high-intensity exercise but could continue with moderate exercise.
5 months after admission	Out of hospital cardiac arrest due to ventricular fibrillation
6 months after admission	Cardiac post-mortem shows subtle cardiomyopathy changes in keeping with a dilated cardiomyopathy
7 months after admission	Genetic tests confirm a positive *LMNA* gene
8 months after admission	Patient's two children and mother seen in the genetics clinic and screening was performed for *LMNA* mutations

Case presentation

A 42-year Caucasian male presented to the acute medical unit with a week's history of lethargy and feeling generally unwell. There was no syncope however he had been intermittently dizzy. He had no past medical history and did not take any regular medications. His father had a history of DCM and had a cardiac resynchronization therapy device with a defibrillator (CRT-D) in situ. He had died the year before at the age of 75. The patient was not a smoker, leading a physically demanding lifestyle. He was not an athletic individual. On presentation, he was haemodynamically stable, and physical examination including cardiovascular auscultation was unremarkable. Laboratory studies revealed normal blood tests including normal renal profile and normal troponin levels. Electrocardiogram (ECG) displayed atrioventricular (AV) block with a Mobitz type I (Wenckebach) pattern at a rate of 40 beats per minute (b.p.m.) with a normal QRS complex and QT interval (*Figure 1*). Chest X-ray was normal and did not show any hilar lymphadenopathy.

He was moved to the coronary care unit for cardiac monitoring and further investigations. Transthoracic echocardiogram was performed and showed the normal left ventricular size and wall thickness. Left ventricular systolic function was normal with an ejection fraction (EF) between 55% and 65% and there was biatrial dilatation.

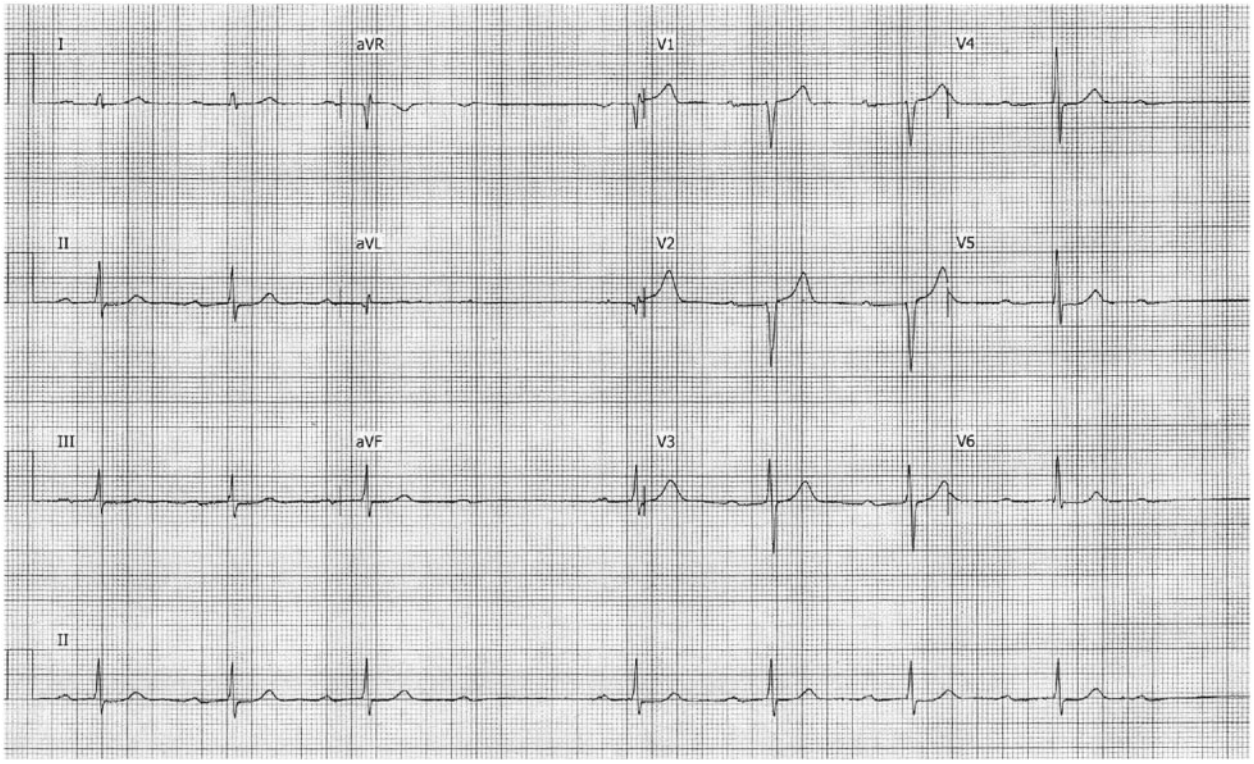


Figure 1 Electrocardiogram on admission to hospital showing atrioventricular block with a Mobitz type I (Wenckebach) pattern at a rate of 40 beats per minute. The QRS duration is narrow, the T waves are normal, and the QT interval is normal.

Overnight cardiac monitoring revealed episodes of non-sustained ventricular tachycardia (VT) (*Figure 2*); however, the patient was asymptomatic. Cardiac magnetic resonance imaging was organized due to the patient's family history and abnormal ECG findings with a suspected diagnosis of laminopathy.

Cardiac magnetic resonance imaging (*Figure 3* and *Video 1*–3) revealed that the left ventricular structure was normal with a normal trabecular pattern. There was mild LV dilatation with an end-diastolic volume of 213 mL (normal 117–200 mL). The EF was calculated at 59%. There was moderate left atrial dilatation, and right ventricular (RV) function was normal. Late gadolinium enhancement (LGE) revealed no evidence of subendocardial scar or transmural injury to suggest ischaemic heart disease. There was a single mid myocardial focus of high signal over the distal RV insertion point inferiorly and a linear area of high signal over the basal septum, findings suggesting DCM.

Local and regional multidisciplinary meetings were conducted over the next few days to discuss the case. The multi-disciplinary meetings consisted of experts in electrophysiology, heart failure, and cardiomyopathy. Laminopathy was considered as the top differential however other differentials included sarcoidosis and amyloidosis. A decision was made to perform genetic testing, a cardiomyopathy screen, and to implant a dual-chamber pacemaker whilst he was an inpatient so that beta-blockers (5 mg) could be initiated to suppress the ventricular arrhythmias. He was discharged home with a plan to be followed up in the cardiology and genetics clinic. The long-term plan was for an upgrade of his pacemaker to an implantable cardiac defibrillator (ICD) if genetic testing identified a pathogenic variant in Lamin A/C.

A few months later he was reviewed in the cardiology clinic and was stable. A pacemaker check revealed that he was ventricular pacing 80% of the time and had 2 brief periods of atrial fibrillation. His CHA_2DS_2-VASc score was 0 so he was not started on anticoagulation. A 12-lead ECG in the clinic showed a high degree of ventricular ectopics so his beta-blockers were up-titrated to 7.5 mg. He had also dramatically reduced his exercise levels since his admission and he was advised to build up his fitness, though not to partake in high-intensity exercise as per ESC guidelines.

In the weeks following his clinic appointment, he unfortunately had an out-of-hospital cardiac arrest whilst walking downstairs in his own home and passed away. A remote pacemaker check was performed which revealed ventricular fibrillation (VF) as the cause of the cardiac arrest. Cardiac post-mortem was performed which showed subtle cardiomyopathy in keeping with a DCM. Genetic tests results were issued a few months later confirming the presence of a pathogenic LMNA mutation. Family screening of the patient's mother, sister, and two young children has subsequently been performed (*Figure 4*).

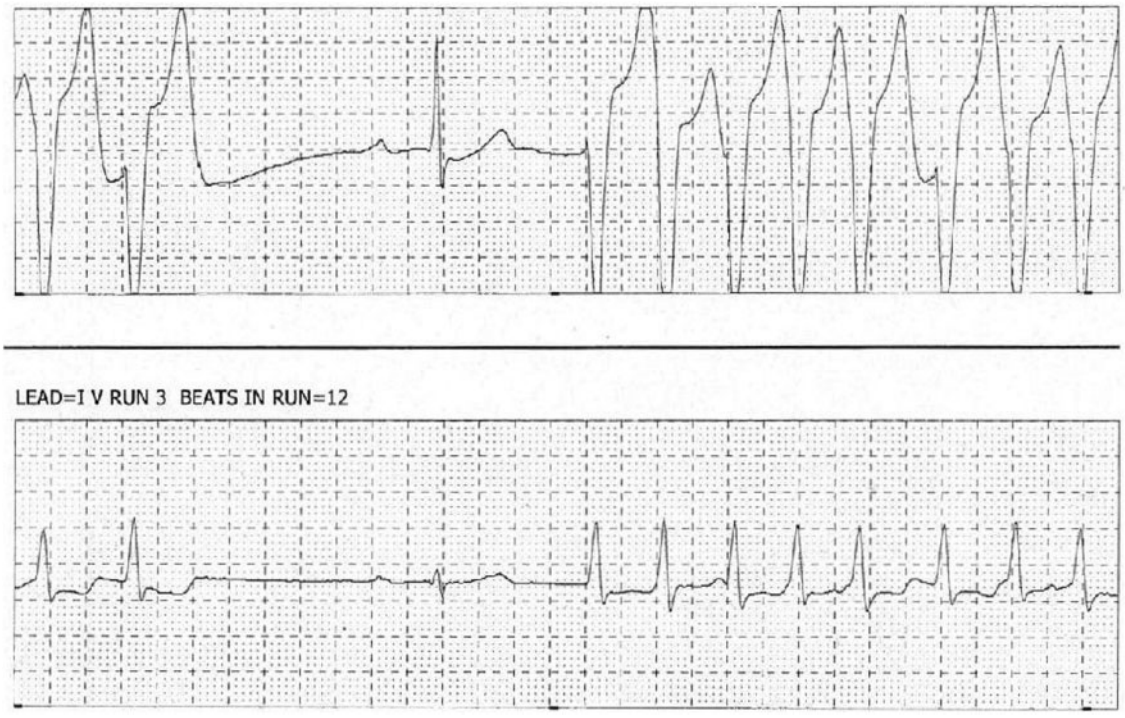


Figure 2 Cardiac monitoring on coronary care unit revealed episodes of non-sustained ventricular tachycardia.

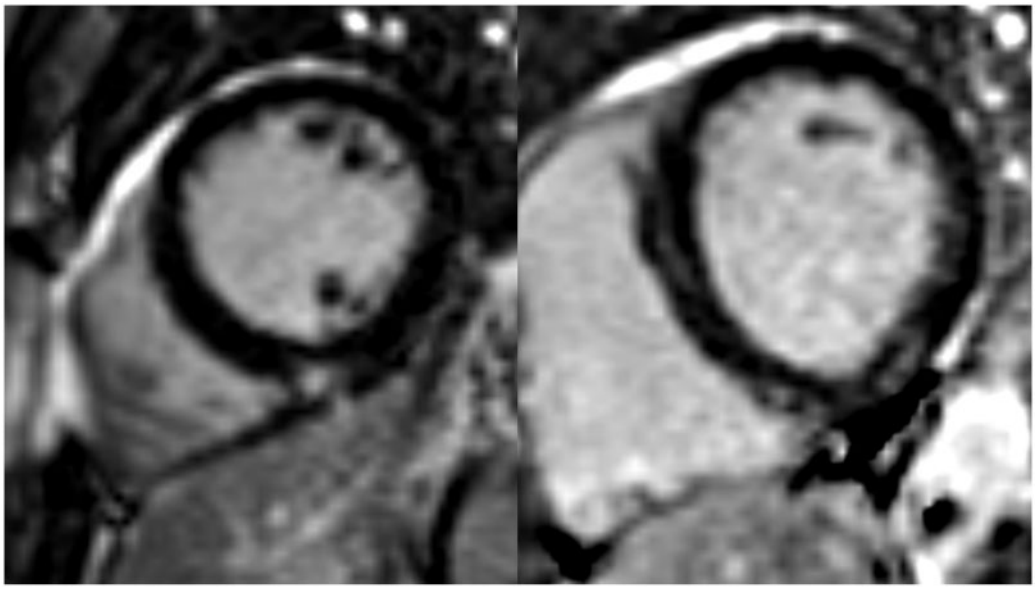
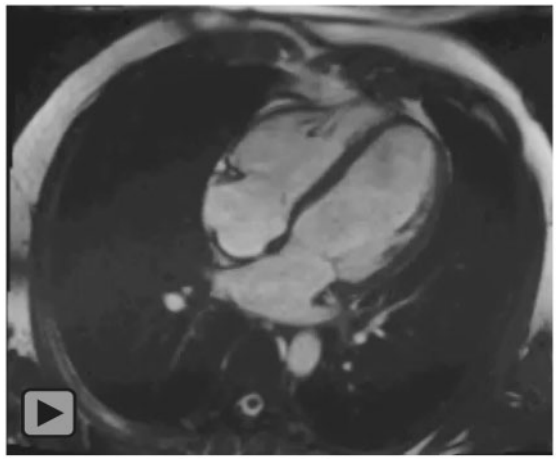
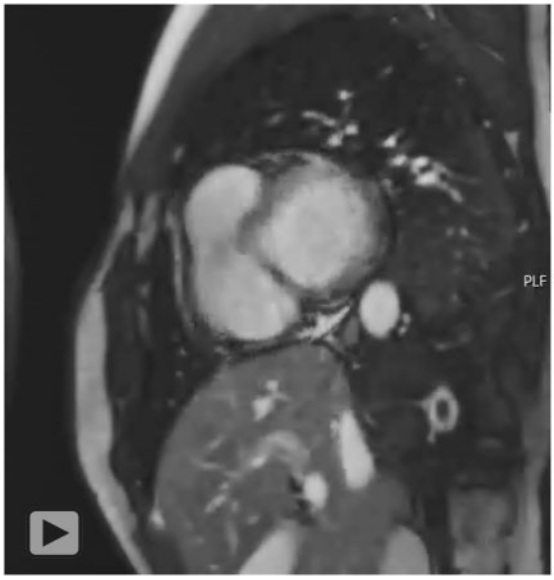


Figure 3 Cardiac magnetic resonance imaging panel showing a single mid myocardial focus of high signal over the distal right ventricular insertion point inferiorly (left image) and a questionable linear area of high signal over the basal septum (right image). Appearances are non-specific but consistent with dilated cardiomyopathy.

Video 1 2 chamber view of cardiac magnetic resonance scan showing normal left ventricular systolic function.



Video 2 Short axis view of cardiac magnetic resonance scan showing normal left ventricular systolic function.



Video 3 4 chamber view of cardiac magnetic resonance scan showing normal left ventricular systolic function, mildly dilated left ventricle and moderately dilated left atrium.

Discussion

LMNA mutations cause up to 10% of DCM.[2] The hallmark of the cardiomyopathy is structural muscle abnormalities and electrical instability leading to aggressive heart failure, life-threatening arrhythmias or even SCD often occurring by middle age.[3,4]

Although only 0.5-5% of patients with DCM show *LMNA* pathogenic variants by genetic analysis, mutations are reported in up to 10% of the familial cases, and up to 33% of the cases of DCM with AV conduction disorders.[4] The pattern of inheritance of *LMNA*-related DCM is autosomal dominant. However, early diagnosis of DCM is often difficult because left ventricle dilatation is mild at the beginning and may remain asymptomatic for many years. *LMNA*-related DCM has a more aggressive course compared to other aetiologies of DCM. This can lead to a higher risk of end-stage heart failure requiring earlier heart transplantation, early-onset conduction disease, and a higher risk of mortality due to ventricular arrhythmias.[3–5]

Electrical dysfunction in laminopathy often precedes the development of a DCM phenotype. Bradycardias manifest as sinus bradycardia, junctional escape rhythms, and will often progress to second- or third-degree heart block.[2] Overall, it is estimated that 44% of patients will eventually need pacemaker implantation after the age of 30 because of bradyarrhythmias.[5,6] Tachyarrhythmias including atrial fibrillation or VT are also an early feature with malignant arrhythmias like sustained VT and VF, are the leading cause of SCD in *LMNA* mutation carriers with cardiac involvement.[5,6]

Symptomatic bradyarrhythmias or even asymptomatic high-degree blocks should be treated with an implantable pacemaker. There is limited evidence to suggest if there is a pacing indication, patients with laminopathies should undergo implantation of an ICD.[7–9] In such cases, especially with young patients, cardiologists face complicated issues regarding optimal management, and the timing for prophylactic ICD implant remains challenging. Implantable cardiac defibrillator implantation in young patients comes with risk. These risks include inappropriate shocks, which is a particular problem in young patients who may be more physically active and thus prone to sinus tachycardia and rates that enter the fast VT or VF zone.[10] A further risk is that of upfront lead complications being greater with high energy leads as

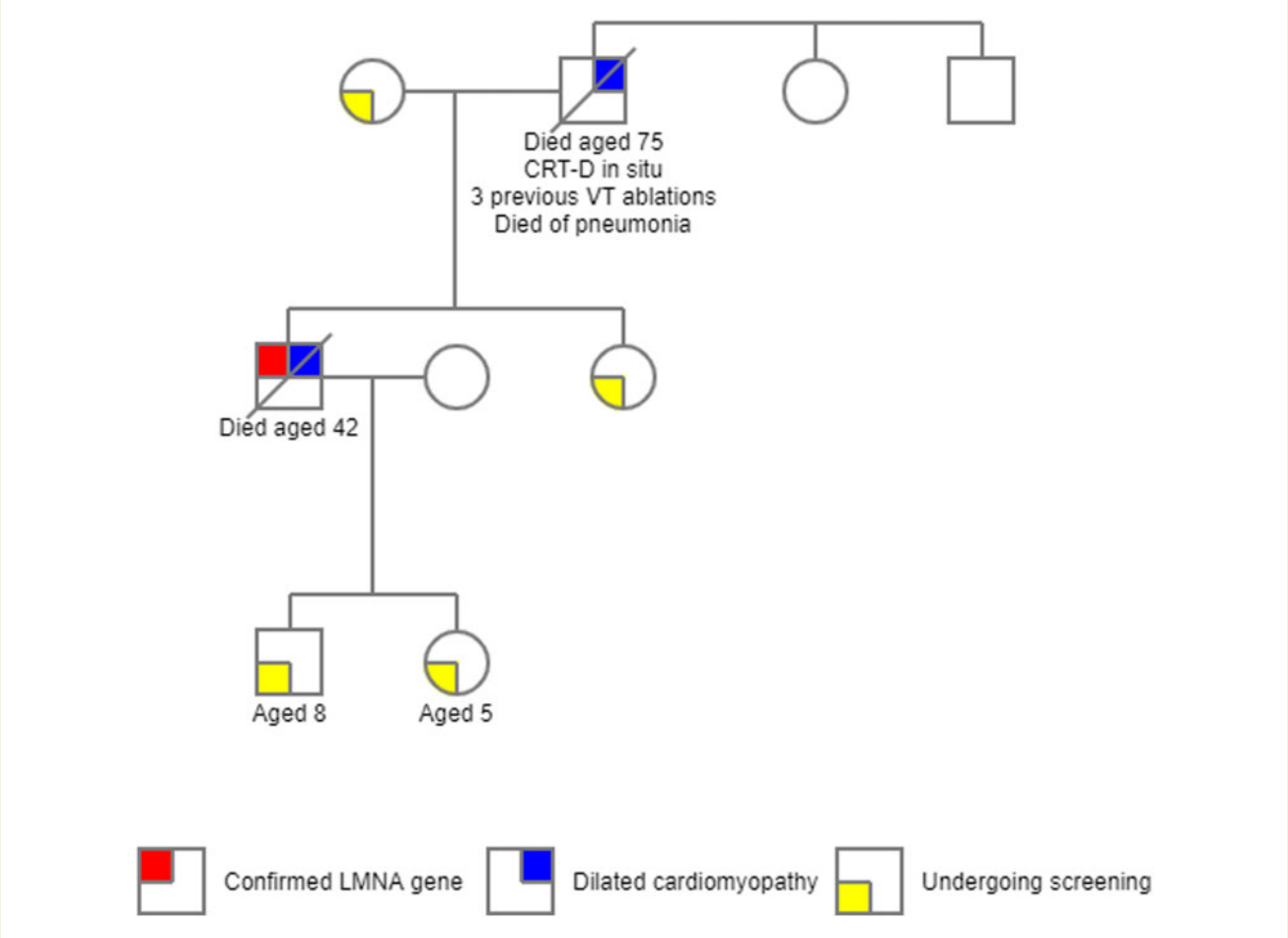


Figure 4 Family pedigree showing three generations of the family. The affected individual's father had a diagnosis of dilated cardiomyopathy and had a cardiac resynchronization therapy device with a defibrillator *in situ*. He died of pneumonia at the age of 75 years. After genetic screening confirmed a positive LMNA gene, the mother, sister, and two children are undergoing screening.

opposed to traditional pacemaker leads and the consideration that the ICD may never be needed.[11] A young patient over the course of their lifetime would need multiple generator changes, decades of surveillance, be at risk for complications, and may never actually need the device.[10–12]

Dilated cardiomyopathy gene panel testing has become a cornerstone of management of inherited cardiomyopathies with implications both for the index case (proband) and their relatives. Significant and likely pathogenic variants in the *LMNA* gene are diagnostic and can have significant implications on the clinical decisions made. In this case, the MDT decision was to wait until a variant was identified before an ICD implant was undertaken due to the uncertainty of the balance of risk and benefit; the malignant nature of inherited cardiomyopathies unfortunately mean that the consequence of this delay (of approximately 3 months) carries extremely high stakes for individual patients. Following from this a crucial aspect of *LMNA*-related DCM is family screening. The condition is autosomal dominant and therefore cardiac assessment and predictive genetic testing should be proposed to all first degree-relatives within the family from the age of 12 years.[6]

Conclusion

This case highlights that patients with laminopathies can have tragic outcomes. This was a young patient presenting with significant bradycardia, AV block as well as evidence of VT, suggesting a variety of dysrhythmias which is a key feature of laminopathies. Cardiac magnetic resonance imaging also showed evidence of LGE suggesting an early cardiomyopathic process despite normal systolic function. The decision regarding device implant was challenging due to the uncertainty of diagnosis until the results of the DCM gene panel were available; this delay unfortunately proved critical. *LMNA*-related cardiac disease is complex and should ideally be managed and followed up in centres with special expertise in inherited cardiomyopathy.

Lead author biography

Dr Gautam Sen graduated in Medicine from Cardiff University, UK, having completed a BSc in Pharmacology. He is training as a Cardiology Registrar in the UK and is currently undertaking a PhD on detecting cardiac inflammation using cardiac MRI and PET-CT at King's College University, London. He holds several roles in relation to medical education and is a sub-editor for the British Society of Cardiology.

Supplementary material

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

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

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