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Original Article

Cardiac manifestations of congenital LMNA-related muscular dystrophy in children: three case reports and recommendations for care

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Abstract Skeletal and cardiac muscle laminopathies, caused by mutations in the lamin A/C gene, have a clinical spectrum from congenital *LMNA*-related muscular dystrophy to later-onset Emery–Dreifuss muscular dystrophy, limb girdle muscular dystrophy, and dilated cardiomyopathy. Although cardiac involvement is observed at all ages, it has only been well described in adults. We present the evolution of cardiac disease in three children with congenital muscular dystrophy presentation of *LMNA*-related muscular dystrophy. In this series, atrial arrhythmia was the presenting cardiac finding in all three patients. Heart failure developed up to 5 years later. Symptoms of right heart failure, including diarrhoea and peripheral oedema, preceded a rapid decline in left ventricular ejection fraction. Recommendations for cardiac surveillance and management in these patients are made.

Keywords: Lamin A/C LMNA; congenital muscular dystrophy; cardiomyopathy; arrhythmia; automatic implantable cardiac defibrillator

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Introduction

Congenital muscular dystrophies are heritable muscle disorders characterised by hypotonia at birth, progressive respiratory insufficiency, contractures, and scoliosis with an estimated point prevalence of 0.5 per 100,000.[1,2] A congenital muscular dystrophy subtype due to *de novo* mutations in the lamin A/C gene (*LMNA*) was first fully delineated in 2008, and is characterised by cervico-axial weakness ("dropped head syndrome"), scapuloperoneal weakness (foot drop), joint contractures, and "rigid spine syndrome" with thoracic lordosis, associated with a dystrophic muscle biopsy and variably elevated creatine kinase levels.[3] In the most severe form, these children present with decreased fetal movement and early lack of motor development. Some may develop head and trunk control and even the ability to walk, followed by progressive loss of motor milestones. There is a high risk of respiratory insufficiency and cardiac involvement as they get older.

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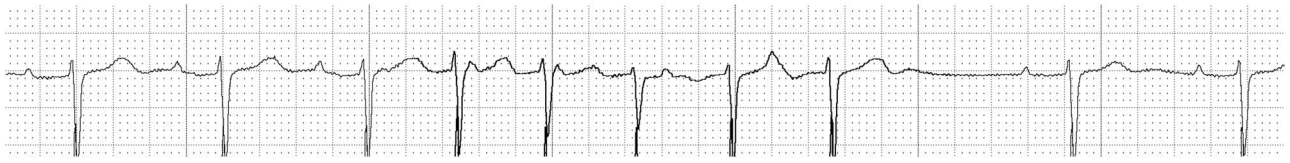

Figure 1.
Tracing from holter monitor showing first degree AV block with short run of atrial tachycardia, age 10.

There is substantial clinical overlap observed among the different subtypes of congenital muscular dystrophy and other early-onset myopathies. A recent international consensus proposed a new nomenclature in which the name of the gene is followed by either "RD" (related dystrophy) or "RM" (related myopathy). The congenital muscle laminopathies due to lamin A/C mutations are thus classified as congenital *LMNA*-related dystrophy (congenital *LMNA*-RD), and account for 6% of congenital muscular dystrophies.[4]

Cardiac involvement in later-onset laminopathies including Emery–Dreifuss and limb girdle muscular dystrophy (LGMD1B) is well described, and includes myocardial dysfunction and arrhythmias, particularly atrial tachycardia and conduction delay, and less commonly ventricular tachyarrhythmia and sudden cardiac death.[5,6] Given the relatively recent description and rarity of congenital *LMNA*-related muscular dystrophy, there are little data on age of onset, cardiac progression, risk of arrhythmias, and sudden cardiac death in this paediatric population. In this case series, we describe the evolution of cardiac disease in three patients with congenital *LMNA*-related muscular dystrophy. Cardiac disease began with atrial tachyarrhythmia, and all three patients manifested striking gastrointestinal symptoms, specifically persistent diarrhoea and abdominal distention, before a precipitous decline in left ventricular ejection fraction and death from heart failure.

Case histories

Patient 1 was born full term and displayed delayed motor milestones during his 1st year of life with elevated creatine kinase of 2100 IU/L. This led to a muscle biopsy, which showed a dystrophic process. He walked from 15 months to 3 years of age with ankle–foot orthoses and thereafter was wheelchair dependent with progressive lordosis. At age 4, a gastronomy tube was placed because of failure to gain weight, and at age 7 he underwent bilateral hip and ankle release surgeries.

He first presented to the cardiology department at 8 years of age because of asymptomatic tachycardia episodes noted on the heart monitor during the orthopaedic interventions. The initial electrocardiogram showed first-degree atrioventricular block with a P-R interval of 200 ms (normal for age <170 ms), occasional premature atrial contractions, and frequent brief runs of ectopic atrial tachycardia (Fig 1). On Holter monitoring, he was in atrial tachycardia 19% of the time, with rare premature ventricular contractions. An echocardiogram showed a left ventricular ejection fraction of 66% (normal 55–70%). A liquid β-blocker preparation was not readily available, and therefore digoxin was initiated with good response, with near-complete resolution of the atrial tachycardia and no initial worsening of the P-R interval.

Over the next 3 years, however, the atrial ectopic rhythm became more frequent, occurring up to 50% of the time, and there was a progressive prolongation of the P-R interval up to 270 ms. Ventricular ectopy also became more complex with 3–4 beat runs of ventricular tachycardia. Digoxin was changed to Atenolol. This also worked well initially, but the arrhythmias continued to worsen over time. His left ventricular ejection fraction remained normal at >70%.

At 12 years of age, a routine Holter monitor showed periods of atrial fibrillation alternating with periods of sinus rhythm with first-degree block (P-R interval of 320–500 ms) and still rare premature ventricular contractions (Fig 2). Anticoagulation was initiated with warfarin. An electrophysiology study revealed a persistent complex atrial tachycardia with atrial fibrillation and atrial flutter. Attempts at direct current cardioversion were unsuccessful at restoring sinus rhythm. B-type natriuretic peptide was minimally elevated at 109 pg/ml (normal <99 pg/ml), and spironolactone was added for presumed underlying cardiomyopathy, despite normal left ventricular ejection fraction. Pulmonary function tests showed restrictive lung disease with forced vital capacity of 1.1 L, 39% predicted (normal ⩾80% predicted). A sleep study showed hypoventilation and obstructive sleep apnoea, and nocturnal bi-level ventilation was initiated. Genetic testing confirmed the diagnosis of congenital *LMNA*-related muscular dystrophy (*LMNA* c.104 T > C; p.Leu35Pro). Given the association with ventricular tachycardia and sudden cardiac death, an implantable cardioverter-defibrillator was placed. He continued on atenolol, warfarin, and spironolactone, as well as received no implantable cardioverter-defibrillator discharges.

About 1 year after implantable cardioverter-defibrillator placement (age 13), he developed atrial

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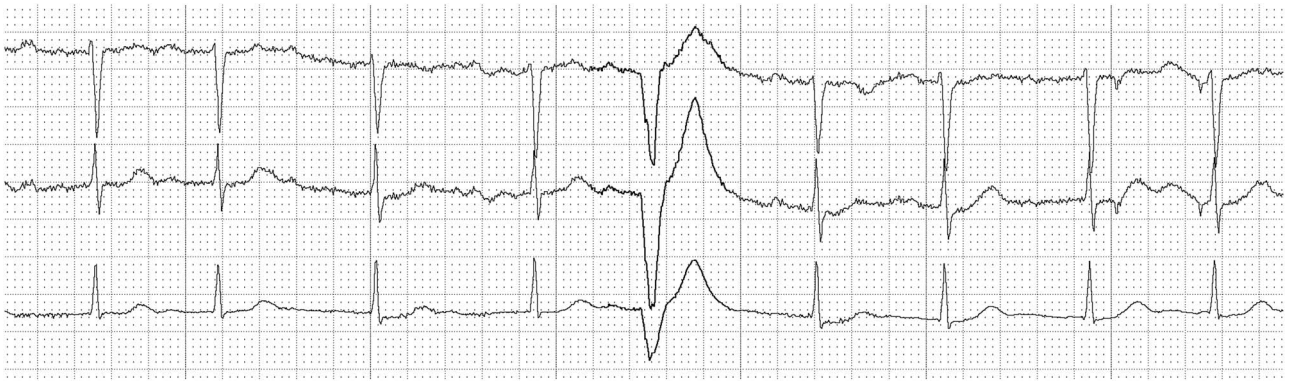

Figure 2.
Tracing from Holter monitor showing atrial fibrillation with a PVC, age 12.

standstill with a junctional rhythm between 40 and 50 beats/minute. Ventricular pacing was initiated at a rate of 75. His left ventricular ejection fraction declined to 51%. He began to have explosive diarrhoea and developed peripheral oedema. His total protein and albumin levels were decreased, liver enzymes were mildly increased, and B-type natriuretic peptide level was 642 pg/ml. A stool sample showed a markedly elevated level of α-1-antitrypsin, confirming the suspected clinical diagnosis of protein-losing enteropathy. The stools initially firmed up with the addition of medium-chain triglyceride oil and the oedema responded to furosemide. Lisinopril and then carvedilol were also added, but his left ventricular ejection fraction declined to 47%, with evidence of diastolic dysfunction and mild dilation of both atria and left ventricle.

Over the next year, he was admitted twice with anasarca, worsening diarrhoea, vomiting, hypoalbuminaemia, and elevated B-type natriuretic peptide with left ventricular ejection fraction remaining in the mid-40s. He was treated with intravenous albumin and furosemide, and started on a high-calorie, high-protein, low-sodium diet, with Elecare supplements. Serum immunoglobulins were noted to be very low and he was treated with intravenous and subcutaneous immunoglobulin.

Oral budesonide was initiated for protein-losing enteropathy at a dose of 9 mg daily. His symptoms of diarrhoea improved significantly and protein-losing enteropathy stabilised for several months. Eventually, oedema, nausea, and poor nutritional status progressed. He developed some shortness of breath, which responded to increased bi-level support during the day. His left ventricular ejection fraction rapidly declined from 27 to 13%. He was then admitted with end-stage heart failure, and passed away in the hospital at the age of 15.5 years after turning off the implantable cardioverter-defibrillator.

Patient 2 presented in infancy with hypotonia, delayed motor development, progressive joint contractures, and spinal rigidity. He walked between 20 and 30 months of age. His creatine kinase level ranged from 1997 to 2296 U/L, and a muscle biopsy showed dystrophic changes. Although his scoliosis progressed to a 70° Cobb angle with significant kyphoscoliosis, surgical intervention was declined. At 14 years of age, he demonstrated restrictive lung disease, with forced vital capacity of 2.3 L, 50% predicted, with nocturnal hypoventilation and sleep apnoea on polysomnography. He was unable to tolerate bi-level ventilation until his admission at the age of 17 years. On routine follow-up at age 16, a Holter monitor showed asymptomatic atrial arrhythmias and non-sustained runs of ventricular tachycardia, and an echocardiogram showed hypokinesis of the basal inferolateral wall and septum with a left ventricular ejection fraction of 55%. A cardiac MRI showed early ventricular fibrosis. Treatment with a β-blocker was declined by the patient because of on-going wheelchair sports participation.

At the age of 17, he presented with progressive chest wall, abdominal, and extremity oedema. He had had a sinus infection and cough 2 weeks earlier, treated with oral amoxicillin. He then developed diarrhoea and increasing shortness of breath. He was admitted after further studies showed a right-sided pleural effusion and free fluid in the pelvis. An electrocardiogram showed rate-controlled atrial fibrillation, and an echocardiogram showed normal biventricular size and systolic function, with mild tricuspid and mitral regurgitation. There were increased left ventricular filling pressures with increased septal E/Ea by tissue Doppler. Holter studies showed persistent atrial fibrillation and runs of non-sustained ventricular tachycardia lasting up to 20 seconds. During this admission, genetic testing was initiated, identifying a variant previously associated with congenital *LMNA*-related muscular dystrophy (*LMNA* c.745 C > T; p.Arg249Trp). The patient was placed initially on diurnal non-invasive ventilation,

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furosemide, and bisoprolol and underwent drainage of the pleural effusion. Serum albumin and total serum protein both during this hospitalisation and a subsequent hospitalisation 6 months later were at the low end of normal levels. Although his laboratory results did not confirm protein-losing enteropathy, steroids were initiated with high-dose methylprednisolone (1 g intravenously daily × 5 days). Diarrhoea responded to steroid treatment. An implantable cardioverter-defibrillator was declined by the patient at that time and he was discharged with maintenance oral prednisone (1 mg/kg daily), nocturnal bi-level ventilation, ramipril, furosemide, and lansoprazole. Steroids were tapered off over 2 months.

The patient re-presented to the hospital 6 months later with oedema and an elevated B-type natriuretic peptide of 3661 (0–300 ng/L). An implantable cardioverter-defibrillator was placed. Bisoprolol was added, and furosemide dosage was increased. There was another hospitalisation 4 months later for oedema, followed by a final hospitalisation after another 5 months with a left ventricular ejection fraction 10–15%, tachypnoea, persistent hyponatraemia, and anuria. A decision was made to turn off the implantable cardioverter-defibrillator and institute comfort measures. The patient died within 12 hours at the age of 18 years in the hospital.

Patient 3 was diagnosed at 2 months of age with congenital muscular dystrophy on the basis of clinical presentation – reduced fetal movement, congenital hypotonia, and motor delay – a slightly increased creatine kinase level (400 IU), and a dystrophic muscle biopsy. He never acquired head or trunk control, and at the age of 2 years he required a tracheostomy and invasive ventilation for early respiratory insufficiency. Genetic testing at the age of 6 years confirmed congenial *LMNA*-related muscular dystrophy (*LMNA* c.1139T > C; p.Leu380Ser). During routine follow-up at 7 years of age, runs of atrial tachycardia were found incidentally on electrocardiogram, initially treated with acebutolol, and then switched to bisoprolol, which was better tolerated. Biannual cardiac studies including electrocardiogram, Holter, and echocardiography were performed without cardiac progression until the age of 12 years, when first-degree atrioventricular block was documented on an electrocardiogram. At this time, the patient developed a period of 2 months of intermittent diarrhoea – 2–3 soft stools per day – with no infectious aetiology identified.

In anticipation of the need for scoliosis surgery at the age of 13 years, a preoperative cardiac workup was performed. The echocardiogram showed normal pulmonary artery pressure and normal left ventricular ejection fraction of 60%. Mild impairment of right ventricular systolic function was detected with a reduced S wave at the tricuspid annulus by tissue Doppler imaging. Electrophysiology testing demonstrated normal infra-hissian conduction and acceleration of the rhythm with isoproterenol. A month before the planned surgery, he presented with abdominal distention and diarrhoea, again without any infectious aetiology identified.

Intra-operatively, the patient became haemodynamically unstable and required resuscitation with fluids and norepinephrine. Broad-spectrum antibiotic coverage was initiated. During the first 48 hours postoperatively, the patient remained haemodynamically unstable with decreased urine output and was given normal saline, albumin transfusions, and norepinephrine. Pedal oedema responded to diuretics; however, 8 days after surgery, acute renal failure was documented and the patient developed clinical findings of right heart failure – lower leg oedema, ascites, and pleural effusions – with an elevated B-type natriuretic peptide, treated with alternating albumin 20% and diuretics. Antibiotics and anti-inflammatory drugs known to be nephrotoxic – aminoglycosides, vancomycin, and non-steroidal anti-inflammatory drugs – were stopped. His left ventricular ejection fraction decreased from 60 to 50%, and dobutamine was added for low cardiac output secondary to right heart dysfunction. The patient experienced nausea and abdominal distention but no diarrhoea. He was discharged 1 month after surgery on diuretics.

After 5 months, aged 14 years, he was re-hospitalised for global heart failure with a restrictive left ventricular filling pattern. He developed continuous diarrhoea with daily soft stools and abdominal distention. It worsened after food intake, leading to decreased oral intake. Laboratory parameters showed hypoalbuminaemia (20–40 g/L), normal prealbumin, and hyponatraemia (124–133 mg/dl). An increase in urine albumin and sodium excretion was detected with further deterioration of his cardiac function and clinical presentation of anasarca. Although protein-losing enteropathy was suspected, laboratory studies showed no steatorrhoea, normal elastase, normal α-1-antitrypsin, and no proteins in the stool. Moreover, treatment with corticosteroids showed minimal improvement with a relapse within 2–3 days of treatment initiation. The patient was discharged home for palliative care and died at the age of 14.5 years at home with his family.

Discussion

This case series describes the cardiac manifestations in 3 children with congenital *LMNA*-related muscular dystrophy, which included progressive atrial arrhythmia, ventricular arrhythmia, conduction system disease, and right and left ventricular dysfunction. Sudden cardiac death has also been described in this population.[3]

The cardiac manifestations are thus remarkably similar to the cardiac findings in adult-onset laminopathies such as Emery–Dreifuss Muscular Dystrophy, although presenting at a much younger age, with a more aggressive clinical course.

In this series, asymptomatic atrial tachyarrhythmias were first detected at ages 7, 8, and 16. Despite medical therapy, one case progressed steadily from intermittent atrial tachycardia, to atrial fibrillation, and finally to atrial standstill with a ventricular escape rhythm. Mild ventricular ectopy and conduction delay with prolongation of the P-R interval were also noted in all three patients. Notably, none of these patients experienced palpitations, dizziness, or syncope. The atrial tachyarrhythmia preceded overt myocardial dysfunction by 5 years in two of the three patients. This highlights the need for routine rhythm surveillance in paediatric *LMNA*-related muscular dystrophy patients, even without cardiac symptoms.

The first echocardiographic changes were not evident until 13–16 years of age, and were initially mild; however, within a few months of the first echocardiographic abnormalities being detected, all three patients rapidly developed right heart failure and gastrointestinal symptoms. This acute decline was precipitated by atrial standstill with junctional bradycardia in one patient, a sinus infection in the second patient, and scoliosis surgery in the third patient. This suggests that physiological stress can lead to further cardiac decompensation. All three worsened steadily despite aggressive management of their congestive heart failure. Left heart enlargement was not as predominant a feature in these patients as often seen in other forms of cardiomyopathy.

Our series is notable in that these patients experienced prominent gastrointestinal symptoms as a manifestation of their heart failure, including diarrhoea, vomiting, abdominal distention, and oedema, although only two of the three had documented hypoalbuminaemia, and only one had confirmed protein-losing enteropathy. Recently, complex interplays between heart failure and the gut have been identified.[7–10] Decreased cardiac function can contribute to reduced bowel perfusion, and thereby impair the function of the intestinal barrier.[8] Several structural changes have been described in the gastrointestinal tract of patients with heart failure, including abnormalities of the gastric mucosa in mosaic pattern in the stomach, antral vascular ectasia, mucosal thickening, and areas of telangiectasias.[9] On the other hand, there is increasing evidence to suggest that a "leaky" bowel wall may lead to translocation of bacteria and endotoxin, which may be an important stimulus for inflammatory cytokine activation in heart failure, leading to a vicious circle.[7,10]

The gastrointestinal symptoms began in our three patients while the left ventricular ejection fraction was fairly well preserved, suggesting that left ventricular systolic function is not a sensitive indicator of disease severity. Diastolic dysfunction and right heart failure play a significant role, and should be evaluated carefully on echocardiogram. Routine measurement of B-type natriuretic peptide may also provide a more sensitive marker for myocardial dysfunction. Gastrointestinal manifestations may precede marked elevations in B-type natriuretic peptide and overt heart failure, and should alert the provider of an impending decline in cardiac status. Pulmonary oedema was not a significant finding in these patients until they were fatally ill.

In adults with *LMNA* disorders, left ventricular ejection fraction <45%, especially in combination with non-sustained ventricular tachycardia, is a known risk factor for sudden death;[6] however, there is an increased risk of sudden death and appropriate discharges in those with implantable defibrillators, even with a normal left ventricular ejection fraction.[5,11] Data are lacking on the risk of sudden death in paediatric *LMNA*-related muscular dystrophy patients. In the original series of congenital *LMNA*-related muscular dystrophy patients described in 2008, one of the 15 died unexpectedly at the age of 3 years, despite a previous normal echo and Holter monitor.[3] In a larger series of LMNA patients from Italy, none of the 18 patients with congenital muscular dystrophy died suddenly.[12] The true risk of sudden death in these young patients is unknown.

Although congenital muscular dystrophy consensus guidelines highlight the need for cardiac surveillance, the recommended frequency of electrocardiogram, echocardiography, and Holter monitoring in initially asymptomatic congenital *LMNA*-related muscular dystrophy children is unclear.[13] On the basis of our own experience and data currently available in the literature, we propose the following recommendations for cardiac surveillance and management in paediatric *LMNA*-related muscular dystrophy patients.

- Baseline electrocardiogram should be performed as soon as the diagnosis is suspected or confirmed, and at least yearly thereafter.
- Periodic Holter monitoring should begin as early as age 5, or any time a rhythm abnormality is suspected, even in asymptomatic patients. Implantation of a loop recorder is an option for rhythm surveillance over an extended period of time.
- Implantable cardioverter-defibrillator should be considered in children with sustained or non-sustained ventricular tachyarrhythmias on ambulatory electrocardiogram monitoring, especially in those with left ventricular ejection fraction <45% or those needing pacemakers for heart block, as in adult-onset laminopathies.[5,6,11]

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- Echocardiography should be performed yearly in younger children, and perhaps more frequently in older children and teenagers, even if there are no cardiac symptoms, especially after the onset of atrial arrhythmias. Careful attention to right heart parameters and diastolic function is necessary. A decline in left ventricular ejection fraction is a late finding, which may not occur until after symptoms of right heart failure develop.
- Yearly B-type natriuretic peptide monitoring should be performed as a marker of myocardial dysfunction, and may be more sensitive than echocardiography.
- During times of physiologic stress such as intercurrent illness, surgery, or a deterioration in rhythm, increased vigilance and evaluation with echocardiography and B-type natriuretic peptide measurement are indicated.
- Aggressive heart failure management should be initiated early, using diuretics, β-blockers, aldosterone antagonists, and angiotensin-converting enzyme inhibitors, although it is unclear whether this alters prognosis.
- Steroids may be considered to treat protein-losing enteropathy or non-specific gastrointestinal symptoms. It is not known whether steroids affect cardiac disease or improve survival, but they may provide symptomatic relief of diarrhoea.
- Initiate a palliative care referral early in the disease process to allow the patient and family to become comfortable with discussions regarding quality of life and prognosis, as well as to express their wishes regarding end-of-life planning.

Vigilant surveillance for rhythm problems and myocardial dysfunction, coupled with early implantation of devices and aggressive medical management, may improve survival. We acknowledge that these recommendations are not based on a large body of evidence, but rather on our own experience caring for a very limited number of patients. These recommendations need to be tested in a prospective cohort analysis.

It should be mentioned that none of the patients in this series had any clinically affected family members, and all three were presumed to have *de novo* mutations, although genetic testing of family members was not performed.

Our series demonstrates that cardiac disease associated with early-onset *LMNA*-related muscular dystrophy can evolve in distressingly malignant ways despite aggressive cardiac management. It is clear that additional treatment strategies still need to be developed. Temsirolimus and Rapamycin – antineoplastic agents that inhibit the mammalian target of rapamycin (mTOR) signalling pathway – and protein kinase inhibitors have been shown to improve heart function in a mouse model of striated muscle laminopathies.[14,15] Gene therapy in LMNA disorders also holds promise for the future.[16]

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Conflicts of Interest

None.

References

1. Sparks S, Quijano-Roy S, Harper A, et al. Congenital muscular dystrophy overview. GeneReviews™, University of Washington, Seattle Washington, 1993-2013.
2. Graziano A, Bianco F, D'Amico A, et al. Prevalence of congenital muscular dystrophy in Italy: a population study. Neurology 2015; 84: 904–911.
3. Quijano-Roy S, Mbieleu B, Bönnemann CG, et al. De novo *LMNA* mutations cause a new form of congenital muscular dystrophy. Ann Neurol 2008; 64: 177–186.
4. Bönnemann CG, Wang CH, Quijano-Roy S, et al. Diagnostic approach to the congenital muscular dystrophies. Neuromuscul Disord 2014; 24: 289–311.
5. Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 2006; 354: 209–210.
6. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers a European cohort study. J Am Coll Cardiol 2012; 59: 493–500.
7. Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, Poole-Wilson PA, Coats AJ, Anker SD. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet 1999; 353: 1838–1842.
8. Krack A, Richartz BM, Gastmann A, Greim K, Lotze U, Anker SD, Figulla HR. Studies on intragastric pCO2 at rest and during exercise as a marker of intestinal perfusion in patients with chronic heart failure. Eur J Heart Fail 2004; 6: 403–407.
9. Raja K, Kochhar R, Sethy PK, Dutta U, Bali HK, Varma JS. An endoscopic study of upper-GI mucosal changes in patients with congestive heart failure. Gastrointest Endosc 2004; 60: 887–893.
10. Sandek A, Anker SD, von Haehling S. The gut and intestinal bacteria in chronic heart failure. Curr Drug Metab 2009; 10: 22–28.
11. Anselme F, Moubarak G, Savouré A, et al. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm 2013; 10: 1492–1498.
12. Maggi L, D'Amico A, Pini A, et al. LMNA-associated myopathies: the Italian experience in a large cohort of patients. Neurology 2014; 83: 1634–1644.
13. Wang CH, Bonnemann CG, Rutkowski A, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol 2010; 25: 1559–1581.

14. Choi JC, Muchir A, Wu W, et al. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin A/C gene mutation. Sci Transl Med 2012; 4: ra102.
15. Ramos FJ, Chen SC, Garelick MG, et al. Rapamycin reverses elevated mTORC1 signaling in lamin A/C – deficient mice, rescues cardiac and skeletal muscle function, and extends survival. Sci Transl Med 2012; 4: 144ra103.
16. Azibani F, Bertrand AT. Gene therapy for *LMNA*-related congenital muscular dystrophy (L-CMD) by trans-splicing. Orphanet J Rare Dis 2015; 10 (Suppl 2): O11.

https://doi.org/10.1017/S1047951116002079 Published online by Cambridge University Press