Cardiac involvement in hereditary myopathy with early respiratory failure
A cohort study

ABSTRACT

Objective: To assess whether hereditary myopathy with early respiratory failure (HMERF) due to the c.951434T>C; (p.Cys31712Arg) TTN missense mutation also includes a cardiac phenotype.

Method: Clinical cohort study of our HMERF cohort using ECG, 2D echocardiogram, and cross-sectional cardiac imaging with MRI or CT.

Results: We studied 22 participants with the c.951434T>C; (p.Cys31712Arg) TTN missense mutation. Three were deceased. Cardiac conduction abnormalities were identified in 7/22 (32%): sustained atrioventricular tachycardia (n = 2), atrial fibrillation (n = 2), nonsustained atrial tachycardia (n = 1), premature supraventricular complexes (n = 1), and unexplained sinus bradycardia (n = 1). In addition, 4/22 (18%) had imaging evidence of otherwise unexplained cardiomyopathy. These findings are supported by histopathologic correlation suggestive of myocardial cytoskeletal remodeling.

Conclusions: Coexisting cardiac and skeletal muscle involvement is not uncommon in patients with HMERF arising due to the c.951434T>C; (p.Cys31712Arg) TTN mutation. All patients with pathogenic or putative pathogenic TTN mutations should be offered periodic cardiac surveillance.

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GLOSSARY
HMERF = hereditary myopathy with early respiratory failure; LV = left ventricular; MFM = myofibrillar myopathy; NIV = noninvasive ventilation; RV = right ventricular.

Hereditary myopathy with early respiratory failure (HMERF) is an autosomal dominant disorder arising due to missense mutations in the fibronectin III domain of the TTN gene, most commonly c.951434T>C; (p.Cys31712Arg). HMERF is characterized by adult onset of distal or proximal muscle weakness in association with early respiratory muscle weakness, which may be the presenting feature and require noninvasive ventilation. Muscle biopsy findings are largely nonspecific, although myofibrillar myopathy and cytoplasmic bodies are described.

Other skeletal myopathies caused by missense mutations in titin include tibial muscular dystrophy due to heterozygous mutations in the C-terminus and limb-girdle muscular dystrophy type 2J arising from recessive mutations at the same locus. Cardiac complications in these phenotypes have not been reported previously. Conversely, heterozygous truncating TTN mutations are a recognized cause of dilated and restrictive cardiomyopathies without apparent skeletal muscle involvement. However, the rare coexistence of skeletal and cardiac muscle disease in recessive truncating titin mutations raises the possibility that cardiac involvement may occur in other titinopathies. This has implications for the surveillance of those at risk. To address this, we carried out the first systematic cardiac study in HMERF using multimodal structural and functional cardiac imaging.
| Patient and family ID | Sex | Age at onset, y | DisD, y | Skeletal muscle pattern | Function | PFTs (% predicted) | Cardiac Hx, lx, and Mx | 12-Lead ECG | Echo summary |
|----------------------|-----|----------------|---------|-------------------------|----------|-------------------|-----------------------|-------------|-------------|
| 1                    | A F | 30             | 14      | Distal LL               | Unaided  | FEV₁  72          | N No medication       | Low-amplitude p waves | Segmental LV hypokinesis and ↓LV EF 50%–55% |
| 2                    | B M | 37             | 6       | Distal > proximal LL > UL | AFO      | FEV₁  52          | 68 N Ramipril for high BP | Normal       | Normal      |
| 3                    | B M | 33             | 13      | Distal and proximal LL and distal UL | Unaided  | FEV₁  83          | 85 Y No medication | Normal       | Grade 1 DD-NFA |
| 4                    | B F | 40             | 10      | Distal and proximal UL and LL and axial | Unaided  | FEV₁  52          | N Propranolol intermittently, 24-hour ECG = 11 beats AT | Tachycardic with premature atrial ectopics | E-E: 8-15, possible diastolic LV dysfunction |
| 5                    | B M | 45             | 2       | Mild distal UL and LL   | Unaided  | FEV₁  67          | 70 N Palpitations; no meds; 24-hour ECG = normal | Normal       | Normal      |
| 6                    | B F | 60             | 14      | Mild distal LL weakness | Unaided  | FEV₁  67          | 62 N No medication | Bradycardic: 55 bpm | E-E: 8-15, possible diastolic LV dysfunction |
| 7                    | B M | 16             | 32      | Distal and proximal LL; distal UL | Stick    | FEV₁  70          | 73 N No medication | Notched p waves | Poor view   |
| 8                    | B F | 29             | 14      | Distal and proximal LL  | Unaided  | FEV₁  70          | 64 Y AVNRT: ablation; no meds | Normal       | Normal (LV EF low normal 55%) |
| 9                    | B M | 35             | 30      | Distal and proximal UL and LL | WC       | FEV₁  33          | 32 Y Lisinopril for high BP | Premature SV complexes | Grade 1 DD-NFA |
| 10                   | B M | 44             | 15      | Distal and proximal UL and LL | WC       | FEV₁  67          | 63 Y Palpitations; atorvastatin | Normal       | Small LV cavity |
| 11                   | B M | 20             | 34      | Distal and proximal UL and LL | Crutch and AFO | FEV₁  57          | 55 N 2012: Perindopril 4 mg, bisoprolol 2.5 mg; 2014: perindopril 4 mg, bisoprolol 5 mg | Low-amplitude p waves, normal PR, flattened T waves (evolving over 2 years) | 2012: LV EF 40%–45%; mild-moderate imp RV; 2013: LV EF 50%; 2014: LV EF >55%, low normal RV function; segmental CM; 2015: LV EF 50% |
| 12                   | B F | 46             | 10      | Distal and proximal LL; distal UL | WC       | FEV₁  73          | 71 N No medication | Premature atrial complexes | Normal       |
| 13                   | C M | 35             | 6       | Distal and proximal LL; proximal UL | WC       | FEV₁  77          | 77 N No medication | Low-amplitude notched p waves, nonspecific flattened T waves (evolving over 3 years) | 2014: LV EF 50%; 2015: LV EF 55% |
| 14                   | C F | NA             | NA      | Nil                     | Unaided  | FEV₁  77          | 77 N No medication | Normal       | Normal       |
| 15                   | D M | 28             | 5       | Distal and proximal UL and LL | AFO      | FEV₁  70          | 70 N No medication | Normal       | Normal       |
| 16                   | E M | 30             | 27      | Distal LL and UL        | uk        | FEV₁  68          | 73 Y No medication | Normal       | Normal       |
| 17                   | F M | 39             | 8       | Distal LL and UL        | uk        | FEV₁  68          | 73 Y No medication | Normal       | Normal       |
| 18                   | G M | 27             | 15      | Distal and proximal LL > distal UL | AFO      | FEV₁  55          | 56 Y No medication | Normal       | Normal       |
| 19                   | H M | 30             | 33      | Distal LL and UL        | uk        | FEV₁  56          | 56 Y SVT, bisoprolol | uk           | uk          |
| 20*                  | I M | 45             | 4       | Proximal and distal LL; proximal UL | Stick    | FEV₁  67          | 71 Y No cardiac hx or medication | uk           | uk          |
| 21*                  | J M | uk             | uk      | Proximal and distal LL; mild proximal UL | uk        | FEV₁  67          | 71 Y PPM, AVR, uk medication | Atrial fibrillation | uk          |
| 22*                  | C M | 44             | 30      | Distal > proximal LL > UL | WC       | FEV₁  33          | 27 Y 2010: Bisoprolol 2.5 mg, furosemide 20–40 mg; 24-hour ECG: AF with variable rate | Atrial fibrillation | 2007: LV EF 45%–50%; 2013: LV EF 50% |

Abbreviations: AF = atrial fibrillation; AFO = ankle foot orthosis; AT = atrial tachycardia; AVNRT = atrioventricular nodal reentrant tachycardia; AVR = aortic valve replacement; BP = blood pressure; bpm = beats per minute; CM = cardiomyopathy; DD = diastolic dysfunction; DisD = disease duration; EF = ejection fraction; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; Hx = history; imp = impaired; lx = investigations; LL = lower limb; LV = left ventricular; Mx = management; NA = not applicable; NFA = normal for age; NIV = noninvasive ventilation; PFTs = pulmonary function tests; PPM = permanent pacemaker; PR = PR interval; RV = right ventricular; SVT = supraventricular tachycardia; UL = upper limb; uk = unknown; WC = wheelchair; * = deceased patients.
METHODS  All participants known to the John Walton Muscular Dystrophy Research Centre, Newcastle upon Tyne, United Kingdom, with the c.951434T>C; (p.Cys31712Arg) TTN missense mutation had a 12-lead ECG and echocardiogram requested as part of routine clinical care. All available cardiac test results were reviewed. Thereafter, all participants residing within the North East of England were invited to attend for a cardiac MRI, irrespective of cardiac symptomatology or initial findings. Where participants were unable to tolerate MRI, cardiac CT scan was offered.

All cardiac MRIs were performed on a 1.5T Siemens MRI scanner using a standardized cardiomyopathy protocol, with black blood anatomical, multiplanar short tau inversion recovery, multiplanar cines—including short axis stack for ventricular function, multiplanar cines, and delayed enhancement sequences obtained with gadoterate meglumine (Dotarem; Guerbet, Villepinte, France). All cardiac CT imaging was performed on a Siemens dual source CT scanner retrospectively gated at low dose for functional information only with a Flash mode delayed enhancement series 7 minutes following iohexol (Omnipaque; GE Healthcare, Cleveland, OH) administration.

Histopathologic correlation. Based on previous reports of desmin as a marker of cardiac dysfunction, we undertook analysis of frozen myocardial samples collected postmortem from 3 patients with HMERF. Immunohistochemistry. Immunolabeling for β-spectrin (clone RBC2/3D5), desmin (DAKO M0760; Glostrup, Denmark), myotilin (NCL-Myotilin; Leica Biosystems, Newcastle, UK), VCP (BD Biosciences, East Rutherford, NJ), ubiquitin (NCL-UBIQm; Leica Biosystems), and p62 (Abcam ab56416; Cambridge, UK) was undertaken.

Western blot. Myocardial samples from patients and age-matched controls with no reported cardiac pathology were homogenized and run on sodium dodecyl sulfate polyacrylamide gel electrophoresis (4%–12% gradient). Immunoblotting was performed using the antibody against desmin. Immunoblots were visualized with SuperSignal West Pico Chemiluminescent Substrate detection using AlphaInnotech FluorChem Q platform and AlphaView software v3.0. All tests were performed in duplicate.

RESULTS  We identified 22 participants with the c.951434T>C; (p.Cys31712Arg) TTN mutation. Three were deceased. Eighteen attended for echocardiogram, of whom 6 subsequently had cardiac MRI and 4 cardiac CT imaging. Two individuals failed to attend planned MRI scans. Cross-sectional imaging was not requested in 7 patients due to geographic dispersion. Clinical features are outlined in table 1. We identified conduction abnormalities in 32% (7/22) of patients. These included sustained atrioventricular tachycardia (8B and 19H), nonsustained atrial tachycardia (4B; figure, A), premature supraventricular complexes (9B), unexplained sinus bradycardia (6B), and atrial fibrillation (21J and 22C). Patients 8B and 19H were treated with bisoprolol and 8B underwent catheter ablation. Patients 5B and 10B had a history of...
palpitations without specific diagnosis being reached despite investigation.

Asymptomatic global left ventricular systolic dysfunction was evident in 4/22 (18%) patients (1A, 11B, 13C, and 22*) on echocardiogram (tables 1 and 2). Although none had chamber dilation, the findings were compatible with nonischemic cardiomyopathy. Two were known to have reduced left ventricular (LV) ejection fraction at study onset (11B and 13C), and one was identified with mild right ventricular (RV) systolic dysfunction in the course of the study (1A). We identified subepicardial fibrosis in 11B on late gadolinium-enhanced MRI (figure, B). None had other lifestyle, history, or medical risk factors to explain their cardiac features.

Four individuals had evidence of possible or definite LV diastolic dysfunction by E-E’ measures on echocardiography. Patient 9B was on maintenance lisinopril for hypertension, but none of the others (3B, 4B, 6B) had any history of cardiac disease, cardioactive medication use, or prior cardiology assessment. Patients 6B and 9B underwent cross-sectional cardiac imaging with CT and mild diastolic impairment was confirmed in 6B (tables 1 and 2).

Response to treatment. Participant 11B demonstrated sustained improvement in cardiac function in the 2012–2015 period following initiation of perindopril and bisoprolol therapy. Left ventricular function improved in patient 22* after commencing β-blocker therapy (table 1).

Relationship to disease onset. The age range of individuals developing cardiomyopathy overlapped with those without (40–65 and 33–65 years, respectively) and with disease duration (6–34 and 2–33 years, respectively). Cardiomyopathy emerged 4–30 years after first skeletal muscle symptoms (table 1).

Relationship to respiratory disease. We assessed the relationship of confirmed ventricular systolic dysfunction at any time with respiratory disease and noninvasive ventilation (NIV) use. No relationship was identified between ventricular systolic impairment and respiratory disease (reduction in pulmonary function tests of 25% or more from predicted) or use of NIV (p = 0.2722 and p = 0.2778, respectively; Fisher exact test).

Histopathologic correlation. Immunohistochemistry. Myocardial tissue preservation was satisfactory in patient 20*; degraded in patient 21* (figure, C); and unsuitable for further analysis in patient 22*. Immunolabeling for myofibrillar proteins was unremarkable and did not demonstrate abnormal protein accumulation (not shown).

Immunoblot. Desmin expression was upregulated (approximately 2.5-fold) in patient 20* compared to controls, suggesting myocardial cytoskeletal remodeling.* Patient 21* showed reduced desmin expression consistent with extensive postmortem delay (figure, D).

DISCUSSION Our findings show that cardiac involvement is not uncommon in patients with the c.951434T>C (p.Cys31712Arg) TTN missense mutation. Conduction abnormalities occurred in a third of patients, with atrial fibrillation and sustained paroxysmal atrioventricular tachycardia most frequently identified (2/22; 9% each). The prevalence of the latter arrhythmia

| Patient and family ID | Rx | LV: Ejection fraction, % | LV: Ejection fraction, % | Fibrosis? | Corrected end LV diastolic volume, mL/m² | Corrected end RV diastolic volume, mL/m² | Overall impression |
|-----------------------|----|-------------------------|-------------------------|----------|-------------------------------|---------------------------------|-----------------|
| 1 A MRI 44 60 N      | 51 (56–96) 63 (48–112) | 1 Subtle dysynchronous ventricular contractions; 2 mild RV impairment |
| 2 B MRI 64 70 N      | 56 (57–105) 59 (61–121) | Normal |
| 5 B CT 57 60 N       | Normal |
| 6 B CT 50 74 N       | Subly abnormal: mildly enlarged atria |
| 7 B MRI 2015 45 53 N | 65 (57–105) 77 (61–121) | Normal (no cardiac medication) |
| MRI 2012 38 45 N    | 90 (57–105) 109 (61–121) | Possible early cardiomyopathy: LVEF and LV volume in URN; no medication |
| 8 B MRI 56 57 N      | 70 (56–96) 69 (48–112) | Normal |
| 9 B CT 63 N          | Normal |
| 10 B CT 72 N         | Normal |
| 11 B MRI 41 60 Y     | 67 (57–105) 92 (55–105) | 1 Subepicardial fibrosis; 2 RV impairment without dilation of RV/PA |
| 13 C MRI 31 38 N     | 49 (47–92) 64 (61–121) | Mild nondilated, nonischemic cardiomyopathy |

Abbreviations: Rx = investigations; LV = left ventricle; LVEF = left ventricular ejection fraction; PA = pulmonary artery; RV = right ventricle; URN = upper range of normal.
is significantly higher than seen in the general population (9% vs 0.2%; p = 0.0026; Fisher exact test).\(^9\)

Additionally, cardiomyopathy was identified in 18% (4/22). Importantly, this was responsive to standard cardiac therapies. Interestingly, the presence of either LV or RV dysfunction was independent of respiratory failure, suggesting the mechanism is not secondary to nocturnal hyperventilation, restrictive pulmonary physiology, or cor pulmonale. The etiology of the diastolic dysfunction observed is uncertain given the absence of LV hypertrophy or significant fibrosis. Diastolic dysfunction is a recognized feature of cardiovascular aging and consequently, is the most likely explanation for our findings. However, a disease-specific association cannot be excluded.

As a recently recognized cause of myofibrillar myopathy (MFM), the TTN mutation causing HMERF is now included in genetic testing panels for MFM.\(^7\) Cardiac involvement in other myofibrillar myopathies, also encompassing arhythmia and cardiomyopathy, is well-recognized, with an estimated prevalence of 30%.\(^9\) Our findings are in keeping with this.

The main limitation of our study is its pragmatic nature as it was conducted in the context of routine clinical health care. Consequently, the echocardiograms were performed and reported by several—albeit experienced—echo-technicians and the CT scans were reported retrospectively. While MRI remains the gold standard investigation for assessment of ventricular function, use of CT in this population, with neurovascular respiratory failure and NIV, enabled more patients to undergo cross-sectional cardiac imaging. Although the 2 modalities are not directly comparable, where imaging is undertaken longitudinally using the same method, an assessment of change can be made.

As the full spectrum of cardiac and skeletal muscle phenotypes associated with TTN mutations remains unknown, patients with pathogenic or putative pathogenic TTN mutations should be offered periodic cardiac surveillance. However, based on the findings we present here, some of the observed abnormalities may be due to normal aging, and not TTN cardiomyopathy per se.

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DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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