





Cardiac and pulmonary findings in dysferlinopathy: A 3-year, longitudinal study

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Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; AV, atrioventricular; BMI, body mass index; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; COS, clinical outcomes study; ECG, electrocardiogram; Echo, echocardiogram; FVC, forced vital capacity; LGMD2b, limb girdle muscular dystrophy 2b; LRTI, lower respiratory tract infection; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MM/MMD1, Miyoshi myopathy; MRI, magnetic resonance imaging; NIV, non-invasive ventilation; NSAD, North Star Ambulatory Assessment for limb girdle type muscular dystrophy; a-NSSA, Amended North Star Ambulatory Assessment; OSA, obstructive sleep apnoea; QTc, QT interval corrected for ventricular rate; RR, relative risk.

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Abstract

Introduction/Aims: There is debate about whether and to what extent either respiratory or cardiac dysfunction occurs in patients with dysferlinopathy. This study aimed to establish definitively whether dysfunction in either system is part of the dysferlinopathy phenotype.

Methods: As part of the Jain Foundation's International Clinical Outcome Study (COS) for dysferlinopathy, objective measures of respiratory and cardiac function were collected twice, with a 3-y interval between tests, in 188 genetically confirmed patients aged 11–86 y (53% female). Measures included forced vital capacity (FVC), electrocardiogram (ECG), and echocardiogram (echo).

Results: Mean FVC was 90% predicted at baseline, decreasing to 88% at year 3. FVC was less than 80% predicted in 44 patients (24%) at baseline and 48 patients (30%) by year 3, including ambulant participants. ECGs showed P-wave abnormalities indicative of delayed trans-atrial conduction in 58% of patients at baseline, representing a risk for developing atrial flutter or fibrillation. The prevalence of impaired left ventricular function or hypertrophy was comparable to that in the general population.

Discussion: These results demonstrate clinically significant respiratory impairment and abnormal atrial conduction in some patients with dysferlinopathy. Therefore, we recommend that annual or biannual follow-up should include FVC measurement, enquiry about arrhythmia symptoms and peripheral pulse palpation to assess cardiac rhythm. However, periodic specialist cardiac review is probably not warranted unless prompted by symptoms or abnormal pulse findings.

KEYWORDS

cardiac, dysferlin, limb girdle muscular dystrophy R2, Miyoshi myopathy, respiratory

1 | INTRODUCTION

Dysferlinopathy is an autosomal recessively inherited form of limb girdle muscular dystrophy, which primarily manifests with skeletal muscle weakness and wasting, caused by the lack of the protein dysferlin.¹ The most common clinical diagnoses associated with dysferlinopathy are limb girdle muscular dystrophy R2 dysferlin related (formerly LGMD 2B) and Miyoshi myopathy (MM or MMD1). The dysferlin protein is highly expressed in skeletal muscle and also in

the myocardium,² leading to concerns that cardiac and respiratory function may be impaired in some patients with this form of muscular dystrophy.

The prevalence of clinically significant cardiac and respiratory dysfunction in dysferlinopathy has generally been considered low.^{3–6} However, small cohort studies and case reports of patients with dysferlinopathy have described occasional cases of cardiomyopathy,^{4,7} asymptomatic left ventricular (LV) dysfunction, LV hypertrophy (LVH),^{3,8} myopathic changes or fibrosis on cardiac MRI,^{9,10} and early

respiratory failure.¹¹ In a recent retrospective cohort series of 48 Japanese patients with dysferlinopathy, 41% had minor cardiac conduction defects and 21% had a reduced forced vital capacity (FVC) of less than 80% predicted.⁵

Rates of cardiac and respiratory dysfunction in patients with dysferlinopathy have not previously been compared systematically to rates seen in the general population. This means that it is not clear whether findings from small case series can reasonably be generalised to the broader dysferlin-deficient population, or if the cardiac or respiratory abnormalities described in case reports had unrelated aetiologies.

The aim of this study is to determine whether dysferlinopathy is associated with an increased risk of cardiac or respiratory abnormalities.

This work adds to the original report from this large internationally recruited cohort of patients with dysferlinopathy¹² by providing 3-y longitudinal follow-up based on repeat testing, and in relating cardio-respiratory findings to objective measures of skeletal muscle function and its progression over the same time period.

2 | METHODS

The protocol and findings at baseline visits have been published previously.¹²

This study was approved by the relevant research ethics committee at each participating institution. Informed consent was obtained from all research subjects.

2.1 | Assessments performed

Medical and family history were collected through patient questionnaires by the site clinicians. This included self-reporting of cardio-respiratory co-morbidities and symptoms, including questions relating to sleep apnoea. All concomitant medications were recorded.

Echocardiograms (echos) at baseline and at 36 mo were performed by experienced cardiac sonographers. The protocol did not dictate a standardised echo examination but simply required the examination used for standard clinical indications at each participating centre. Some, therefore, reported a larger range of parameters than others. Technical issues related to positioning of less mobile participants and reduced echo windows meant that not all measures were obtainable from all examinations in some participants.^{13,14} Standard 12-lead electrocardiograms (ECG) were performed at the same visits. Ventricular rate and PR intervals were obtained from ECGs at each local site. ECGs were then scanned and transmitted centrally. A more detailed analysis and reporting of ECGs was performed by a neuromuscular cardiologist centrally. Reports included assessments of P-wave amplitude, morphology and axis, QRS axis and duration, and QT intervals. The QTc interval presented in this paper was the one calculated automatically by the ECG machine using Bazett's correction. ECGs with measurement values outside the normal range were re-

checked manually. Baseline and 36-mo traces were then compared to determine consistency of any initial abnormalities and any new changes that developed over time.

Experienced physiotherapists undertook spirometry to measure FVC at each of six patient evaluation visits (screening, baseline, 6, 12, 24, and 36 mo). Assessment of change in FVC between sitting and lying was also measured, starting from year 2. Particular note was made of those with an FVC below the lower limit of normal (80%).¹⁵

To correlate heart and respiratory measures with skeletal muscle function, we used the North Star Ambulatory Assessment for limb girdle type muscular dystrophy (NSAD score).¹⁶ This scale was adapted from the a-NSAA for use in ambulant and non-ambulant patients with dysferlinopathy. The NSAD scale was validated using the baseline visits in the Jain COS study and was then used to provide direct motor assessment scores by experienced physiotherapists for subsequent assessments. The full NSAD score was therefore available at year 3, but not at baseline, for correlation with cardiac and respiratory measures.

2.2 | Statistical analysis

Means and paired t-tests were used to compare normally distributed FVC data between visits in the patients with FVC results at both baseline and at year 3. Non-normally distributed QRS duration was compared using Wilcoxon signed rank test between those with and without LV dysfunction or LVH.

Chi-squared testing was used to look for significant relationships between reported symptoms, low FVC, and any cardiac abnormality at baseline. To determine independent risk factors for baseline abnormalities, factors showing an association on Chi-squared testing were combined with age and body mass index (BMI) into a binary logistic regression model for each cardiac abnormality and FVC. To review the relationship with functional ability, modelling was repeated with year 3 data and with the NSAD score.

For longitudinal comparisons, only patients who completed both assessments were included.

3 | RESULTS

Baseline demographics and findings in the 188 study participants are summarised in Table 1. Two patients died between baseline and their planned year 3 assessment: one, aged 88 y, of pneumonia and the other, aged 68 y, of unknown cause.

3.1 | Baseline cardiac symptoms

At least one potentially cardiac symptom was reported by almost half of patients at baseline (Table 1). Breathlessness was frequently reported by ambulant but not non-ambulant patients and was more common in older ambulant patients with a higher BMI (Supporting

TABLE 1 Cardiac and respiratory parameters at baseline according to age

| Parameter | Median age in years at baseline | | | | | | | | | | | |
|--------------------------------------|---------------------------------|----|----------------|----|----------------|----|----------------|----|------------------|----|-----------------------------|-----|
| | Under 30 (N = 51) | N | 30–39 (N = 53) | N | 40–49 (N = 42) | N | 50–59 (N = 31) | N | Over 59 (N = 11) | N | All ages combined (N = 188) | N |
| Median age in years (range) | 25 (11–29) | 51 | 34 (30–39) | 53 | 45 (40–49) | 42 | 53 (50–59) | 31 | 64 (60–86) | 11 | 37 (11–86) | 188 |
| Median BMI kg/m ² (range) | 24 (17–26) | 46 | 25 (15–50) | 47 | 23 (17–38) | 39 | 25 (16–33) | 30 | 24 (19–41) | 6 | 24 (15–50) | 168 |
| Male gender | 28 (55%) | 51 | 24 (45%) | 53 | 21 (50%) | 42 | 12 (39%) | 31 | 3 (27%) | 11 | 88 (47%) | 188 |
| Ambulant ^b (%) | 49 (96%) | 51 | 40 (75%) | 53 | 30 (71%) | 42 | 22 (71%) | 31 | 5 (45%) | 11 | 146 (78%) | 188 |
| FVC (L) | 4.16 | 50 | 4.08 | 52 | 3.63 | 41 | 3.27 | 30 | 2.40 | 11 | 3.77 ± 1.07 | 184 |
| Mean (sd) | ± 1.10 | | ± 0.87 | | ± 0.98 | | ± 0.97 | | ± 0.68 | | | |
| FVC (% predicted) | 94 (38–116) | 50 | 95 (56–125) | 52 | 91 (46–140) | 41 | 89 (49–131) | 28 | 80 (43–105) | 11 | 92.00 (38–140) | 182 |
| NIV users ^a | 0 (0%) | 51 | 1 (2%) | 53 | 2 (5%) | 41 | 1 (3%) | 31 | 0 (0%) | 11 | 4 (2%) | 188 |
| Echo “abnormal” ^a | 8 (17%) | 46 | 6 (12%) | 52 | 8 (21%) | 39 | 9 (32%) | 28 | 6 (60%) | 10 | 37 (21%) | 175 |
| LVEF <55% | 4 (9%) | 43 | 6 (14%) | 44 | 3 (8%) | 35 | 2 (7%) | 27 | 2 (25%) | 8 | 17 (11%) | 157 |
| LVEF <50% | 1 (2%) | 43 | 0 (0%) | 44 | 2 (6%) | 35 | 0 (0%) | 27 | 0 (0%) | 8 | 3 (2%) | 157 |
| LVH ^a | 2 (5%) | 41 | 1 (2%) | 41 | 1 (3%) | 32 | 5 (21%) | 24 | 2 (22%) | 9 | 11 (8%) | 146 |
| P-wave abnormality | 17 (65%) | 26 | 15 (48%) | 34 | 13 (57%) | 23 | 12 (67%) | 18 | 4 (50%) | 8 | 61 (58%) | 106 |
| QRS >120 ms | 0 (0%) | 37 | 1 (3%) | 39 | 1 (3%) | 29 | 1 (5%) | 20 | 1 (14%) | 7 | 4 (3%) | 132 |
| Hypertension ^a | 3 (6%) | 51 | 3 (6%) | 53 | 11 (26%) | 42 | 6 (19%) | 31 | 4 (36%) | 11 | 27 (14%) | 188 |
| Palpitations | 5 (10%) | 51 | 3 (6%) | 53 | 9 (21%) | 42 | 5 (16%) | 31 | 1 (9%) | 11 | 23 (12%) | 188 |
| Ankle swelling | 6 (12%) | 51 | 11 (21%) | 53 | 12 (29%) | 42 | 11 (35%) | 31 | 8 (73%) | 11 | 48 (26%) | 188 |
| Breathlessness | 9 (18%) | 51 | 9 (17%) | 53 | 12 (29%) | 42 | 8 (26%) | 31 | 1 (9%) | 11 | 39 (21%) | 188 |
| Dizzy episodes | 5 (10%) | 51 | 6 (11%) | 53 | 7 (17%) | 42 | 4 (13%) | 31 | 2 (18%) | 11 | 24 (13%) | 188 |
| Fainting history | 2 (4%) | 51 | 0 (0%) | 53 | 1 (2%) | 42 | 0 (0%) | 31 | 0 (0%) | 11 | 3 (2%) | 188 |
| Sleep apnoea | 3 (6%) | 51 | 2 (4%) | 53 | 4 (10%) | 42 | 4 (13%) | 31 | 2 (18%) | 11 | 15 (8%) | 188 |

^aFactors that showed significant association with age in binary logistic regression modelling.

^bAmbulant patients were those who reported not using a wheelchair full time at the time of assessment.

Information Table S1, which is available online). Patients who reported any of these non-specific symptoms were not more likely to have echo or ECG abnormalities than those who were asymptomatic (Supporting Information Table S1).

Leg swelling was more common in non-ambulant than in ambulant patients, but was not associated with cardiac abnormalities (Supporting Information Table S1). Hypertension was the most frequent cardiovascular co-morbidity identified, increasing in incidence with age (Table 1) but not independently related to muscle function at year 3 (Supporting Information Table S1).

3.2 | Cardioactive medications

Thirty-six (19%) participants were taking one or more cardioactive medications for diagnoses other than dysferlinopathy. These included hypertension, arrhythmias, ischemic heart disease, diabetes mellitus, and leg oedema. In none was therapy initiated for LV dysfunction. Medications listed were ACE-inhibitors (ACEi) or angiotensin receptor

blockers (ARBs), beta-blockers, diuretics, anti-platelets or anti-coagulants, statins, calcium channel blockers, and other anti-arrhythmic drugs. Between baseline and 3-y assessments, eight patients had ACEi, beta-blocker, calcium channel blocker, or diuretics initiated and another three had the doses of pre-existing medications increased.

3.3 | Baseline ECG findings

Of the 180 baseline ECGs performed (Figure 1), 177 (98%) were in sinus rhythm and 3, aged 54, 67 and 71 y, respectively, were in atrial fibrillation (AF) with controlled ventricular response rates. The PR interval was abnormally short (i.e., <120 ms) in six and abnormally prolonged in three (PR intervals 204–230 ms) of the 168 ECGs where PR interval was recorded at site (Table 2).¹⁷ All three had either long-standing hypertension and/or coronary artery disease (2) or prior myocardial infarction (1) accounting for the atrioventricular (AV) block. QRS-duration was greater than 120 ms in four patients who had hypertension or old myocardial infarction (Table 2). None of the six

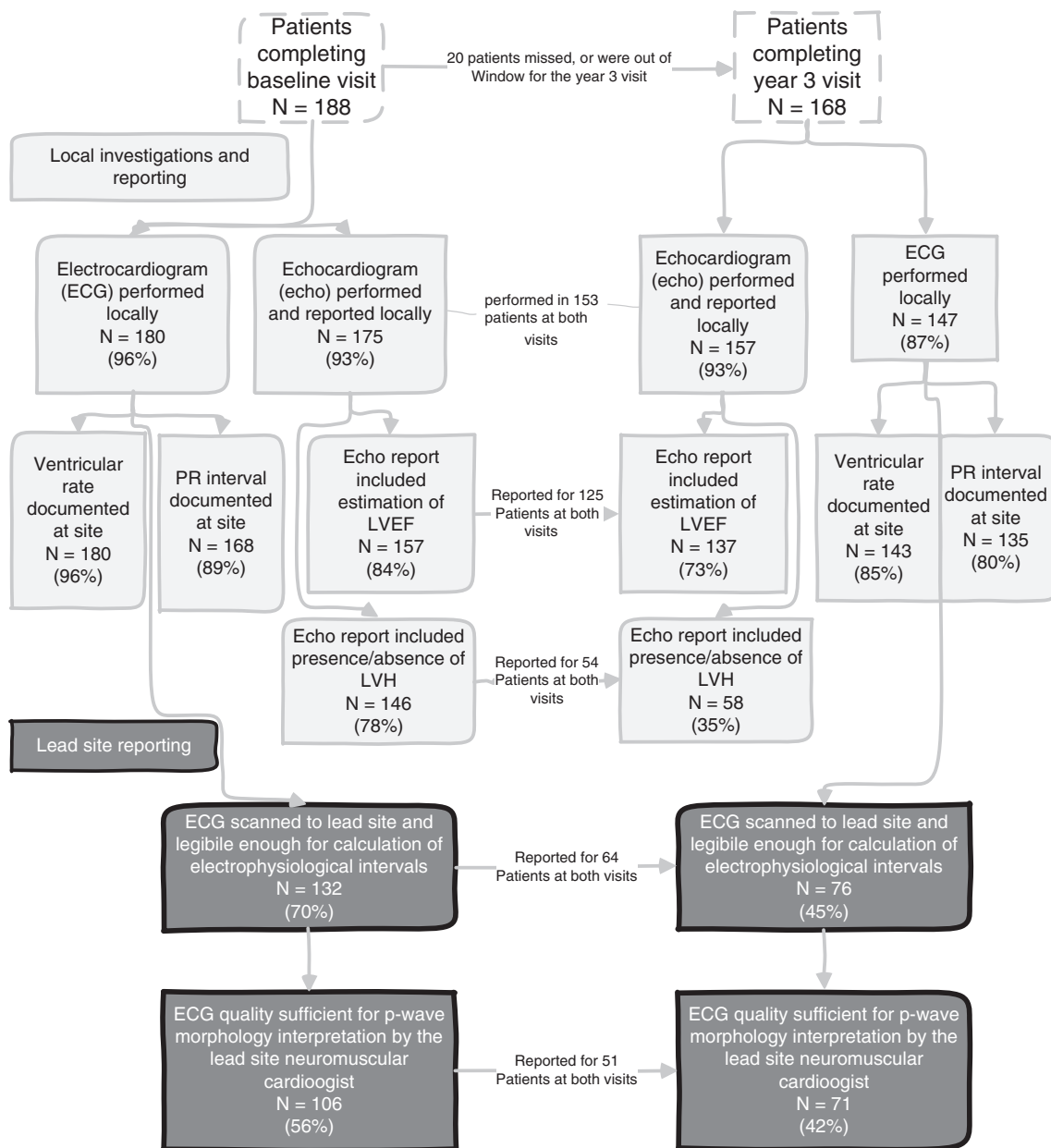


FIGURE 1 Flow chart of cardiac assessments included in analysis

ECGs, identified by automated reporting as showing QTc interval prolongation, were confirmed on manual re-measurement.²¹

ECG trace quality and scan resolution were variable, such that full interpretation of all ECGs was not possible (Figure 1). In the 106 baseline ECGs legible enough for P-wave morphology interpretation by the lead site neuromuscular cardiologist, one or more P-wave abnormalities were evident in 61 patients (58%) (Table 1). Abnormalities comprised low-amplitude, peaked or varying P-wave morphology in 14 (13%), prolonged P-wave duration in 36 (34%), or P-wave notching in 23 (22%) (Supplementary Figure S1). The finding of abnormal P-waves did not correlate with echo measures of atrial enlargement, reduced LV-ejection fraction (LVEF <55%), LVH, or diastolic dysfunction. Prevalence of abnormal P-waves did not increase with age (Table 1) or BMI and were not more common in subjects with known

hypertension, nor in those reporting palpitations or other, potentially cardiac, symptoms (Supporting Information Table S1).

3.4 | Changes in ECG findings between assessments

Of the 64 patients whose ECGs were available from both assessments (Figure 1), 62 showed sinus rhythm and 2 (3%) (aged 54 and 71 y) AF at both visits. Another patient (aged 67 y), who was in AF at baseline, died of unknown cause before having the repeat recording. Of the 51 patients with ECGs available from both assessments, P-waves had become abnormal in 6 but initial abnormalities were not reported in 9 (Table 3).

TABLE 2 ECG parameters at baseline and normal ranges

| | N | Median (range) | Normal range ^{a,b} | Patients below normal range (%) | Patients above normal range (%) |
|------------------------|-----|----------------|------------------------------------|---------------------------------|---------------------------------|
| Sinus rate (beats/min) | 180 | 71 (46–150) | 60–100 | 5 (3) | 3 (2) |
| PR interval (ms) | 168 | 150 (110–230) | 120–200 | 6 (4) | 3 (2) |
| QRS duration (ms) | 132 | 92 (70–145) | 70–120 | 0 (0) | 4 (3) |
| Bazett's QTc (ms) | 131 | 417 (362–570) | 350–450 (male) 350–470 (female) | 0 (0) 0 (0) | 4 (6) 2 (3) |

Abbreviation: IQR, interquartile range.

Note: All durations are given in milliseconds (ms).

^aBorys Surawicz TK, Chou's Electrocardiography in Clinical Practice. 6th edition. 2008.

^bViskin S. The QT interval: too long, too short or just right. Heart Rhythm. 2009;6:711–715.

TABLE 3 Cardiac and respiratory parameters of patients with assessments at both visits

| | Baseline | | Year 3 | | Number tested at both visits |
|--------------------------|----------------|------------------------------|----------------|------------------------------|------------------------------|
| | Median (range) | Mean ± SD Patient number (%) | Median (range) | Mean ± SD Patient number (%) | |
| Demographics | | | | | |
| Age (y) | 37 (11–71) | | 40 (14–74) | | 168 |
| % male | 46% | | 46% | | 168 |
| BMI (kg/m ²) | 25 ± 5.9 | | 26 ± 6.2 | | 153 |
| Motor function | | | | | |
| NSAD score | Not performed | | 14 (0–54) | | 159 (y 3 only) |
| Ambulant (%) ^ | 131 (78) | | 125 (75) | | 168 |
| Respiratory | | | | | |
| FVC (L) | 3.80 ± 1.04 | | 3.67 ± 0.98 | | 162 |
| % predicted FVC | 90 ± 18 | | 88 ± 19 | | 162 |
| Sitting – Lying drop (L) | Not performed | | –0.08 ± 0.24 | | 153 (y 3 only) |
| Nocturnal NIV | 4 (2%) | | 7 (4%) | | 163 |
| Sleep apnoea | 13 (8%) | | 11 (7%) | | 167 |
| Morning headaches | 13 (8%) | | 24 (14%) | | 167 |
| Frequent LRTI | 6 (3%) | | 2 (1%) | | 167 |
| Cardiovascular | | | | | |
| Echo “abnormal” | 30 (20%) | | 17 (11%) | | 153 |
| LVEF <55% | 10 (8%) | | 9 (7%) | | 125 |
| LV hypertrophy | 3 (6%) | | 4 (7%) | | 54 |
| P-wave abnormality | 33 (65%) | | 30 (59%) | | 51 |
| QRS > 120 ms | 3 (5%) | | 3 (5%) | | 64 |
| Hypertension | 21 (12%) | | 24 (14%) | | 168 |
| Palpitations | 20 (12%) | | 23 (14%) | | 167 |
| Leg swelling | 39 (23%) | | 55 (33%) | | 167 |
| Breathlessness | 35 (21%) | | 34 (20%) | | 166 |
| Dizzy episodes | 19 (11%) | | 24 (14%) | | 167 |
| Syncope | 3 (2%) | | 2 (1%) | | 167 |

3.5 | Arrhythmia prevalence

A prior history of arrhythmias was reported by eight patients at baseline (4%): AF in three (the same three in whom it was noted on ECG), sinus

tachycardia in one, ventricular ectopy in one, and “unspecified” in three. Six of the patients reporting arrhythmias had other co-morbidities including hypertension (four), sleep apnoea requiring NIV (one), and mitral stenosis (one). Abnormal echos were also noted in three. The patient with

sinus tachycardia showed a LV impairment with reduced ejection fraction. One patient with AF (aged 54 y) had mitral stenosis, pulmonary hypertension, and left atrial dilatation on echo, while another (aged 67 y) had a LV impairment with reduced ejection fraction.

3.6 | Baseline echo findings

LV systolic dysfunction (LV ejection fraction <55%) was found in 17 (11%) subjects. LV fractional shortening and chamber dimension were within population normal ranges (Supporting Information Table S2).¹⁸ LVH was found on 11 baseline echos. Its prevalence increased with age (relative risk [RR], +0.1/y) and increasing BMI (RR, +0.14/unit) but not with hypertension ($p = 0.45$) or diabetes mellitus ($p = 0.24$). Left atrial enlargement was found in 11 patients and right atrial enlargement in 4. Echo abnormalities were more common in older patients (RR, 0.05/y) and in those with a higher BMI (RR, 0.12/unit), but were not independently associated with skeletal muscle function, as measured by NSAD scoring, at the year 3 assessment.

3.7 | Changes in echo findings between assessments

Echo abnormalities were seen in 30 patients at baseline. These were all graded as mild and resolved by year 3 in 13 (43.3%) (Table 3). Eleven of these patients were already on cardiac medications, and five others had medications added between the two assessments. In four, resolution of abnormality coincided with the introduction or adjustment of anti-hypertensive medications. However, abnormal findings had resolved without therapy changes in 13, including borderline low LVEF in one. New abnormalities developed in four patients: LA dilatation in two, LV diastolic dysfunction in one, and concentric LV-remodelling in one.

3.8 | Respiratory findings

Mean FVC was mildly reduced at baseline and fell by 2% of the predicted value by year 3 (Tables 1, 3). An FVC of <80% was observed in 44 patients (24%) at baseline and 48 patients (30%) by year 3. A sitting to lying drop in FVC of more than 0.5 L was observed in six patients (4%) at year 3, and five of these also had an FVC of <80%.

In a model of percent predicted FVC with patient age, BMI, disease duration, and NSAD score, only the functional ability denoted by the NSAD score was significantly related to FVC (Figure 2). Supporting this, FVC was lower in non-ambulant patients (mean FVC = 81.6%, median age 45) than in those with retained ambulation (mean FVC = 92%, median age 35) ($p < 0.01$) at baseline. However, although there was a significant positive correlation between a lower NSAD score and lower FVC, variability in FVC measures between those of the same functional level was common (Figure 2). FVC of <80% predicted was found in 27 ambulant patients at baseline. Respiratory co-morbidities did not account for the lower measures and, although seven patients (4%) had asthma and one had chronic obstructive pulmonary disease (COPD), the FVC in these eight patients was >80% predicted. Symptoms of nocturnal hypoventilation (morning headaches, frequent lower respiratory tract infections [LRTIs] and/or breathlessness)^{19,20} were not reported more frequently in those with a lower FVC.

Non-invasive ventilation (NIV) requirement was rare, with a small increase by the year 3 assessment (Table 3). A diagnosis of “sleep apnoea” was reported by six of these seven patients and COPD in one patient. These seven patients, aged 19–55 y (median, 34.5 y), had more advanced muscle weakness, as evidenced by an NSAD score of 12 or less. A low FVC of <80% was seen in six of these NIV users. However, neither NSAD scores nor spirometry measures were *independent* predictors of NIV use at the year 3 assessment. NIV treatment at year 3 was independently associated with increasing patient age (RR, +0.1/y) and higher BMI (RR,

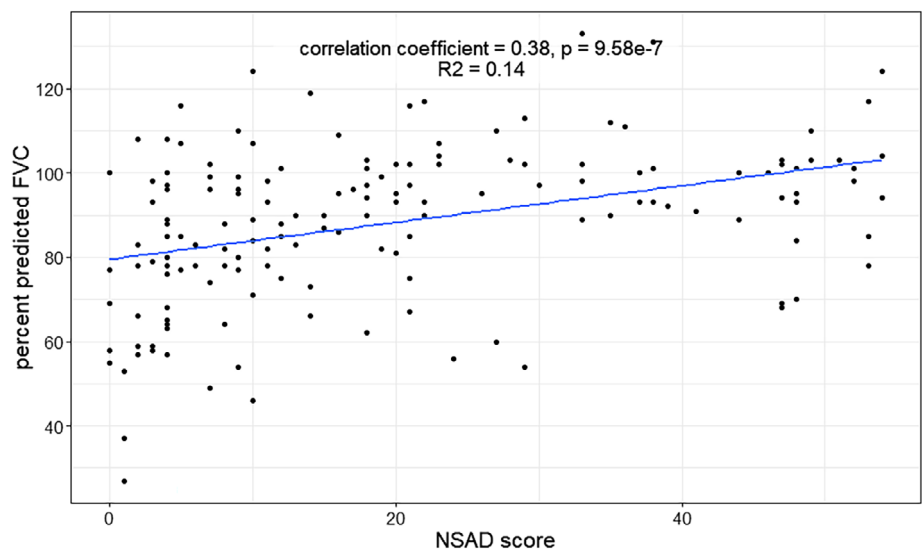


FIGURE 2 Correlation between skeletal muscle function and respiratory assessment. NSAD score: NSAD is an objective functional scale. Percent predicted FVC: FVC result expressed as a percentage of normal for an age- and height-matched population. Correlation coefficient: Pearson's correlation coefficient. R2: coefficient of determination

+0.14/unit), and six of the seven patients were significantly overweight (BMI, 32.2–51.9).

4 | DISCUSSION

The main findings from this cohort of patients were, first, that 24–30% had respiratory impairment as assessed by FVC of <80% predicted, without alternative explanation, and second, 58% had atrial electrical abnormalities as evidenced by P-wave abnormalities on surface ECGs at baseline.

Reduced FVC measures were mostly seen in non-ambulant patients, supporting findings of a previous Japanese study.⁵ However, FVC was also reduced in some ambulant patients with no identifiable co-morbidities, suggesting that reduction in respiratory reserve can be part of dysferlinopathy, perhaps relating to mild diaphragmatic dystrophy.^{5,21} Patients with respiratory impairment rarely reported symptoms of respiratory insufficiency, demonstrating that symptoms alone should not be used to monitor respiratory function. Assessment of respiratory muscle strength, with sitting and lying FVC measurement, should therefore be included in surveillance of these patients. However, since respiratory function did not decline significantly between assessments, FVC monitoring once every 2 y should be sufficient to detect significant changes.

Despite identifying some patients with low FVC, advanced respiratory impairment requiring NIV does not seem to occur in dysferlinopathy. The prevalence of sleep apnoea in this cohort is no higher than in the general population.²² UK guidelines recommend continuous positive airway pressure (CPAP) for symptomatic patients with moderate or severe obstructive sleep apnoea (OSA),²³ giving a CPAP use prevalence in the general population similar to that seen in this study. NIV requirement can be due to obstructive or restrictive causes or a combination of both.²⁴ In other forms of muscular dystrophy with respiratory involvement, increasing diaphragmatic involvement contributes to a restrictive respiratory impairment as disease progresses²⁰ and this has been suggested in dysferlinopathy.²¹ However, in this cohort, NIV use was not frequent, even in those with advanced skeletal muscle involvement. Those who did require NIV were more likely to be older with a higher BMI or have COPD, factors that are related to OSA and NIV use in the general population.²⁵ This suggests that NIV requirement was of obstructive cause and unrelated to dysferlinopathy, although it is possible that mild diaphragmatic involvement is compounding hypopnoea in these patients and contributing to NIV requirement.

Dysferlinopathy does not appear to be associated with cardiac co-morbidities or symptoms in this cohort. Although hypertension was frequent, it was not more common than in the general population.²⁶ Leg swelling was commonly encountered in non-ambulant patients, but did not appear to be related to cardiac function and is well known to occur in cases of reduced mobility of many causes.²⁷ Breathlessness was the only potentially cardiac symptom that was reported more frequently than in the general population.²⁸ We postulate that this may be related to the increased exertional

demands of remaining ambulant with worsening muscle function, rather than of cardiac aetiology, particularly as these breathless patients tended to be older with a higher BMI than those not reporting breathlessness and were not more likely to have echo or ECG abnormalities.

The main cardiac abnormality identified was of atrial electrical conduction, evidenced by dysmorphic P-waves observed at higher rates than in the general population.²⁹ Prolonged P-waves indicate slowed electrical conduction across and between atria and have not been reported previously in dysferlinopathy patients. The findings are compatible with an atrial electropathy being part of the dysferlinopathy phenotype.^{29,30} In cohort studies, unrelated to muscular dystrophy, prolonged, notched, or otherwise dysmorphic P-waves on ECG are associated with the development of atrial tachyarrhythmias (atrial tachycardia, flutter, or fibrillation).^{31,32} Sinus node disease and atrial tachyarrhythmias are a well-recognised part of other muscular dystrophies, such as Emery-Dreifuss muscular dystrophy.³² The clinical implication for patients with dysferlinopathy is that they may be more prone to develop AF. However, the RR does not appear to be high, as the prevalence of AF at baseline was not higher than in the adult population in the USA.³³

While progressive abnormalities in AV and infra-Hisian conduction are seen in patients with myotonic dystrophy, laminopathies, and in some muscular dystrophies, this was not found in this dysferlinopathy cohort.^{34,35} Although PR prolongation and bundle branch block were noted in a minority of our cohort, this was only in association with co-morbidities. We therefore conclude that these abnormalities were unlikely to be attributable to dysferlinopathy.^{5,17} On the basis of the echo findings of the study, any structural abnormalities were either inconsistent or mild and of doubtful clinical significance or explained by subject age or known co-morbidities. Clinically significant cardiomyopathy, as opposed to atrial electropathy, is probably not part of the dysferlinopathy phenotype.

4.1 | Limitations of the study

This observational study was conducted over a period of 3 y, which is a relatively short period of follow-up for patients with a slowly progressive condition. Longer follow-up may allow more definitive conclusions and identification of additional risk factors for progression in respiratory or cardiac conduction deficits.

From a respiratory perspective, the diagnosis of sleep apnoea and ventilation need was self-reported. While we conclude that cases requiring ventilation were most likely obstructive in nature, rather than due to diaphragmatic or intercostal weakness, a definitive conclusion would require more detailed respiratory assessment, including polysomnography, to determine the cause.

From a cardiac perspective, while we identified frequent dysmorphic P-waves that may increase the risk of atrial arrhythmias, we did not include Holter-ECG monitoring in our study. The 1.7% prevalence of AF in this population may, therefore, be an underestimate, as it does not capture patients with intermittent or non-

sustained AF. We plan to assess AF risk further in a sub-study that will include signal averaging of P-wave and Holter-ECG recordings.

Two patients died during the study. We were unable to clarify the cause of death in the younger patient (aged 68 y) and cannot definitively state whether it had a primary cardiac or respiratory cause. Allowing for previous known medical history, however, we consider death directly due to dysferlinopathy unlikely.

5 | CONCLUSIONS

In this large, multi-national cohort of patients with dysferlinopathy, severe respiratory muscle weakness was rare, but mild impairment was sufficiently common to justify screening for it routinely at follow-up by FVC measurements every 2 y. Dysferlinopathy did not cause clinically significant LV dysfunction or LVH. However, more than half of the patients showed atrial electrical conduction abnormalities on ECG. An atrial electropathy seems to be part of the dysferlinopathy phenotype; so, patients may be at increased risk of developing AF compared to the general population. We recommend routine enquiry about arrhythmia symptoms at neuromuscular reviews, routine pulse checking for asymptomatic AF and standard Holter ECG testing, if pulse abnormalities are detected or when palpitation symptoms are reported. However, specialist cardiac review and more detailed testing is probably not warranted unless prompted by symptoms or abnormal pulse findings.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CONFLICTS OF INTEREST

This study was financed through a grant from the Jain Foundation. Apart from this grant, none of the authors has any conflict of interests to disclose.

DATA AVAILABILITY STATEMENT

Anonymised aggregate data will be provided on reasonable request. Requests should be made to the clinical outcomes study steering committee by contacting the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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