

PREVALENCE OF CARDIOMYOPATHY IN DUCHENNE AND BECKER'S MUSCULAR DYSTROPHY

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Background: Cardiac assessment was not done routinely in Duchenne (DMD) and Becker muscular dystrophy (BMD) patients in Northern region of England while evidence was gathering on progressive cardiomyopathy in these patients. We wanted to find out the prevalence, progression and clinical features of cardiac involvement in Duchenne and Becker muscular dystrophy. **Methods:** It is a retrospective review of clinical, electrocardiographic and echocardiographic assessments. **Results:** The notes of 52 Duchenne and Becker muscular dystrophy patients were reviewed out of which 32 had DMD, 6 had Intermediate muscular dystrophy (IMD) and 14 had BMD. Prevalence of preclinical and clinically evident cardiac involvement was 88.4% in DMD and BMD patients. Sixty nine% of patients had clinically evident cardiac involvement but only four patients had cardiac symptoms in the form of palpitations, out of which two were due to respiratory dysfunction and others was due to cardiac failure. Clinical examination of the rest of all of the patients was unremarkable. Electrocardiogram was abnormal in 88.4% of patients. Conduction defects were found in 19.4% of patients. Echocardiogram was abnormal in 80.7% of patients but all were poor echo subjects including those who had normal echocardiogram. **Conclusions:** Though most patients were asymptomatic, a high percentage had evidence of preclinical and clinically evident cardiac involvement. So in all patients with Xp21 linked muscular dystrophy a routine baseline cardiac assessment should be done at the age of 10 years and reviewed after intervals of one to two years.

Keywords: Duchenne muscular dystrophy (DMD), Becker's muscular dystrophy (BMD), Intermediate muscular dystrophy (IMD), Cardiomyopathy, Dystrophin, Cardiomyopathic index, Echocardiographic window.

INTRODUCTION

Duchenne and Becker muscular dystrophies are a group of X-linked recessive neuromuscular diseases characterised by progressive muscular weakness and wasting. In Duchenne muscular dystrophy (DMD), weakness is usually noted from two to five years of age and the child becomes wheelchair bound at around 9 to 12 years and death occurs in early third decade. In Becker muscular dystrophy (BMD) muscle weakness starts in the second decade and patients become wheelchair bound in the third decade and death occurs in the fourth decade or later.¹ Fifteen percent of patients fall in to an intermediate category, where onset of weakness is at the age of 7-9 years and wheelchair dependency occurs at the age of 14 to 17 years and death occurs in the third or fourth decade.

The gene involved in DMD and BMD is the 'dystrophin gene, largest of all the genes ever found spanning 2.5 mega bases.² Deletions are the most common mechanism to cause the disease (60% cases). Point mutations account for up to 20% to 30% of mutations and duplications up to 6%.³

Cardiomyopathy

Cardiac involvement in DMD was first described in 1836 and now it has been found to be a common finding in most generalised myopathies.⁴ Cardiac involvement in DMD and BMD patients has been reported in the range of 84%-96% irrespective of age.^{5,6} Cardiomyopathy follows a course from preclinical to

clinically evident stage and ends in dilated cardiomyopathy and cardiac failure.⁶⁻⁹

Cardiac involvement in DMD and BMD can be diagnosed in preclinical stages by minor instrumental signs.^{9,10} As most of the patients remain asymptomatic until the later stage of dilated cardiomyopathy, frequent cardiovascular follow ups can improve their management by keeping an eye on their cardiomyopathic progress and early treatment.^{4,11}

PATIENTS AND METHODS

A total of 162 case histories of patients who were under follow up or who had recently died were reviewed retrospectively at Newcastle General Hospital (from Nov 2002 to July 2003), to find patients who had either undergone a cardiac assessment by a cardiologist or had, at least an ECG and Echocardiographic examination.

After reviewing all these case histories 52 patients with cardiac investigations were found which included 32 DMD, 6 IMD and 14 BMD. Thirty-two out of 52 patients had had a detailed cardiac assessment by a cardiologist and 20 had had only an ECG or echocardiogram. ECGs of the patients, who had not been examined by a cardiologist in the past, were examined by the cardiologist during this study. QT intervals were measured by a computer programme at Freeman Hospital while other measurements such as PQ segment, R and S wave, were done by hand lens. Cardiac status of these patients was classified as:

1. **Normal:** When there were no signs and symptoms on clinical examination and no electrocardiographic and echocardiographic abnormality.
2. **Mildly abnormal or preclinical:** No signs and symptoms on clinical examination but when there were minor instrumental signs such as:
 - (a) Tall R waves in lead V1, giving an R/S ratio greater than 1.
 - (b) PQ segment shorter than normal and QT segment longer than normal (as related to heart rate) which in turn increases the electrocardiographic cardiomyopathic index. QT/PQ.⁶
 - (c) Q waves in lateral and inferolateral leads giving a false picture of myocardial infarction⁷.
 - (d) Mild echocardiographic abnormalities as mildly depressed left ventricular function.
3. **Moderately abnormal:** When there were signs and symptoms of cardiomyopathy and in addition to parameters of preclinical status, involvement of conduction system (e.g., bundle branch block), P wave, T wave, ST segment changes and moderately abnormal echocardiography, e.g., moderately depressed left ventricular function.
4. **Severely abnormal:** When there were signs and symptoms of heart failure, above mentioned electrocardiographic changes, dilated cardiac chambers (related to age and weight), abnormal 48 hour tape, abnormal ECG gated pool blood scan.

RESULTS

Thirty two DMD patients were aged between 14 and 21 years and 6 intermediate muscular dystrophy patients were aged between 19 and 31 years, while BMD patients were aged between 22 and 59 years. Each group had distinct clinical course. DMD patients had age of onset of weakness from 1½ to 5 years and age of wheelchair confinement was from 8 to 12 years. At the time of investigations no patient was ambulant.

The BMD patients had age of onset from 20 to 28 years and only four of the 14 patients were wheelchair bound (at the age of 50 years), rest were ambulant. As the name suggests the intermediate muscular dystrophy group was intermediate in clinical course with the age of onset from 8 to 9 years and wheel chair dependency at the age of 14 to 17 years.

Clinical assessment:

Sixteen patients had had a previous ECG at the time of diagnosis so comparison was possible with subsequent ones. In others only single assessment was available. The results of the cardiac assessment are shown in Table-1.

Table-1: Cardiac assessment

Disease	DMD	IMD	BMD
Number	32	6	14
Age (years)	14-21	19-31	22-59
Normal	2	0	4
Pre-clinical	10	0	0
Moderately Abnormal	8	6	6
Severely Abnormal	12	0	4

Clinical examination was done by a cardiologist on 32 patients and was unremarkable on 28 patients. Only 4 patients had symptoms of palpitations and two patients had signs of heart failure, e.g., raised JVP, diffused apex beat, oedema, and basal crepitations. One patient had cyanosis. All DMD and intermediate patients had spinal deformities ranging from moderate to severe scoliosis. In the BMD group only one patient had scoliosis but this was of mild degree.

Electrocardiography:

Only two of 32 DMD patients had a normal ECG at the age around 18 years, four of fourteen BMD patients had a normal ECG at the age of 39, 41, 45 and 53 years respectively. Rest of all had some ECG abnormality.

Cardiomyopathic Index (QT/PQ):

The QT/PQ ratio was increased in 46 of 52 patients (88.4%) (as related to heart rate). This was due to the combination of a prolonged QT interval and shortened PQ segment, as summarised in Table-2.

Table-2: ECG cardiomyopathic index as related to heart rate

	No. of cases	HR (bpm)	QT (ms)	PQ (ms)	QT/PQ (ms)	Normal (ms)
DMD	4	60-75	350-372	40	8.75-9.3	7.38
	28	75-100	312-420	30-60	6.2-10.4	6.72
IMD	2	60-75	412	50	8.24	7.38
	4	75-100	320	30-40	8-10.6	6.72
BMD	6	60-75	366-400	50	7.32-8	7.38
	8	70-100	339-440	40-100	4.4-9.75	6.72

R wave in Lead V₁:

Eighty-seven percent (28) of DMD patients had prominent R waves in lead V₁. The R/S ratio was >1 in 24 and equal to 1 in 4. In the BMD group 2 patients had prominent R wave and R/S ratio more than one and 1 had equal to 1. In IMD group only 3 patients had R/S ratio more than one.

Q wave abnormalities:

Forty percent (13) of DMD patients had Q waves in the lateral and inferolateral leads. Four patients of the intermediate group had Q waves in leads I, AVL, V₅, V₆ and same patterns of Q waves was present in ECGs of 4 BMD patients. Q waves are suggested to be an important finding in preclinical cardiac involvement in DMD, BMD and even in carriers at an early age.^{12,13} Figure-1, 2 and 3 show Q waves in the ECGs of DMD patients.

P wave abnormalities:

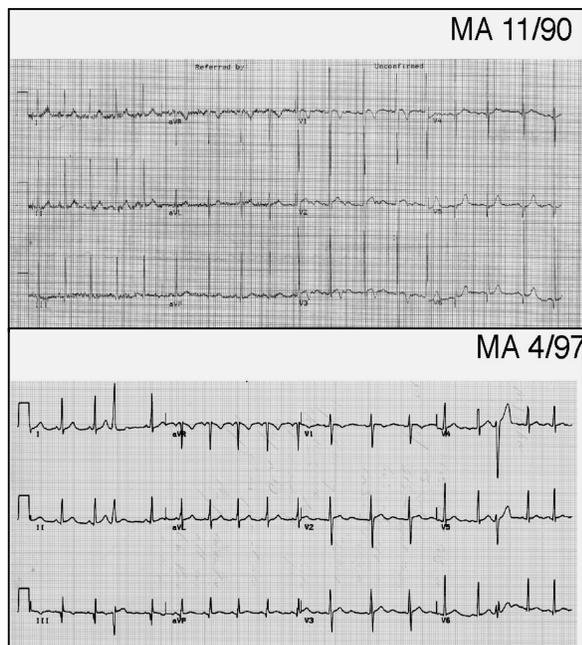
Sixty-eight percent (22) of patients in DMD group had P wave abnormalities. These consisted of prolonged P waves, notched or peaked P waves indicative of left and right atrial hypertrophy respectively.

T wave abnormalities:

Sixty-two percent (20) of DMD patients had repolarization abnormalities. These consisted of low amplitude T waves, bifid T waves. In the IMD only one patient had T wave abnormalities and no abnormal T waves were found in the BMD group. T-wave abnormalities are shown in Figure-1, 2 and 3.



Figure-1: DMD: Pathological Q waves in leads I/AVL/AVV4-V^ and diffuse repolarization (T-wave) abnormalities



Figures-2 and 3: DMD: Two ECGs 7 years apart showing evolution of pathological Q waves and repolarization abnormalities

U wave:

Twenty-five percent (8) patients with DMD had prominent U waves at the age of 15 to 18 years, however whether this relates to age, general frailty or

is evidence of a repolarisation abnormality is uncertain.

Right ventricular hypertrophy (RVH)

Twenty-five percent (8) patients in the DMD group fulfilled the criteria of RVH, by showing tall R waves in the right sided precordial leads and R/S >1, with T waves and ST segment depression. One patient in the intermediate group showed features of RVH.

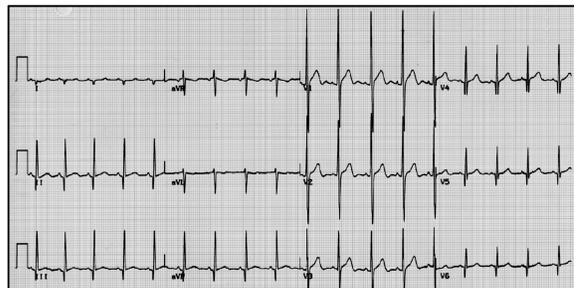


Figure-4: DMD: ECG Showing prominent R waves in right precordial leads and R-S ratio >1

Left ventricular hypertrophy (LVH)

Six-patients (18.7%) in the DMD group showed evidence of LVH as indicated by abnormally tall R waves, inverted T waves, depressed ST segments and Q waves in AVL and left precordial leads. QT intervals were also prolonged. None of the intermediate or BMD patients had ECG evidence of LVH.

Conduction defects:

Eight-patients (25%) in the DMD group, one in the intermediate and one in BMD, had partial Right Bundle Branch Block (RBBB). Clinical and electrocardiographic data is summarised in Table-3.

Table-3: Clinical and electrocardiographic data

	DMD	Intermediate	BMD
Total number of patients	32	6	14
Symptoms	4 (12%)	0	0
Signs	4 (12%)	0	0
Spinal deformity	32 (100%)	6 (100%)	2 (14%)
Normal ECG	2 (6%)	0	4 (28%)
Abnormal ECG	30 (94%)	6 (100%)	10 (71%)
Sinus rhythm	24 (75%)	5 (83%)	13 (93%)
Sinus tachycardia	2 (6%)	0	0
QRS pattern: Right axis deviation	8 (25%)	0	0
Left axis deviation	0	0	0
Prominent R wave in V ₁	28 (87%)	3 (50%)	3 (21%)
R/S ratio >1	24 (75%)	3 (50%)	2 (14%)
Q waves in leads I, II, AVL, V ₅ -V ₆	13 (40%)	4 (67%)	4 (28%)
Abnormal P waves	22 (69%)	4 (67%)	0
Abnormal T waves	20 (62%)	1 (16%)	0
U waves*	8 (25%)	0	0
RVH	8 (25%)	1 (16%)	0
LVH	6 (19%)	0	0
Partial RBBB*	8 (25%)	1 (16%)	1 (7%)

*Clinical significance unknown

Holter monitoring:

Infrequent ventricular ectopic beats were identified in 4 DMD, 4 intermediate and 2 BMD patients on 48-hour

Holter recordings. The remainder had normal 48-hour tapes.

Atrial flutter:

Despite the P wave abnormalities referred to above, only one patient with DMD had a short lasting episode of atrial flutter.

Echocardiography:

The quality of echocardiograms obtained was poor due to the fact that the majority of patients had limited echo windows for examination. Due to overall immobility many could not be adequately positioned to obtain the standard range of imaging views. Within limitation of this, ventricular function was graded crudely for each patient in to one of four categories: normal, mildly abnormal, moderately abnormal and severely abnormal.

Normal: Two patients in the DMD and four in BMD group had normal echocardiography, although all of them were poor echo subjects. The rest of the patients had some echo abnormality.

Mildly abnormal: Ten patients out of 32 (31%) DMD patients had mildly depressed left ventricular (LV) function.

Moderately abnormal: Eight patients (25%) in DMD group had moderately abnormal echo results having moderately depressed LV function and global hypokinesia. Four IMD patients had lateral and posterior wall hypokinesia, and two had septal hypokinesia. In the BMD group six patients had moderately depressed LV function

Severely Abnormal: The remaining 12 patients (37%) in the DMD group had dilated left ventricle and global hypokinesia. Four of the BMD patients had severely abnormal LV function.

Signal averaged ECG:

Signal averaging of the ECG is done to more accurately define QRS duration and to determine the presence of late potentials. To date only two patients of the DMD group had undergone this investigation and all of their findings were normal.

ECG gated pool blood scan (Radionuclide Ventriculography):

This was performed in patients with severely depressed LV function to qualify the abnormality more accurately for future comparisons of the effects of therapy. Only two patients of the DMD group had undergone this investigation and had confirmed dilated cardiomyopathy with an ejection fraction of 20%.

Previous cardiac investigations:

Until recently, cardiac assessment was not performed routinely in patients with skeletal muscular dystrophy. So only some of the patients had previous

cardiac assessment in the form of an ECG only which showed important features. Sixteen of 32 DMD patients had previous ECGs for comparison with index cardiac assessment, out of which 6 had the same ECG changes as the most recent one, 8 to 10 years later, six had Q waves laterally and prominent R waves in previous ECGs 7 to 9 years before this index cardiac assessment, while 4 had previous normal and recent abnormal results after 10 to 12 yrs.

DISCUSSION

The prevalence and timing of onset of cardiomyopathy in DMD and BMD has received little attention despite the recognised association.^{6-9,14-18} We found a high frequency of electrocardiographic and echocardiographic evidence of important preclinical and clinically evident cardiac involvement in these patients which coincides with previous reports⁵⁻⁸, confirming the need for routine cardiac assessment in these patients.

The study is a retrospective examination of a small core of patients with Duchenne, Becker and Intermediate forms of skeletal muscular dystrophy. The study has many limitations including, the small core of patients studied, the fact that patients were screened at a variety of ages and a variety of stages in the course of their skeletal dystrophy. It was not possible for this report to perform serial assessments of all patients, nor were all cardiac assessments uniformly performed or reported. A key limitation was the quality of transthoracic echocardiographic examinations obtained for technical reasons. The results therefore represent a preliminary assessment of the role of the cardiac screening of patients with skeletal muscular dystrophy for the presence of concomitant cardiomyopathy.

Despite all these limitations, the results are important and point the way towards a more definitive cardiac evaluation of these patients based on the experiences obtained to date.

Clinical examination of most of the patient was unremarkable. Only four out of 52 patients had cardiac symptoms in the form of palpitations, out of which two were found to be due to respiratory dysfunction and the others were due to cardiomyopathy. All the patients who developed dilated cardiomyopathy remained asymptomatic until later stages of heart failure which accounted for their delayed diagnosis. It is suggested that physical limitations imposed by skeletal muscle disease in DMD protects the individual against the demands that may lead to cardiac symptoms.¹⁴ However, four Becker muscular dystrophy patients with dilated cardiomyopathy were ambulant and did not experience much physical limitations yet they remained asymptomatic.

Palpitations with dyspnoea may be the earliest symptoms of cardiac failure but this may be caused by respiratory dysfunction.¹¹ A detailed assessment of both cardiac and respiratory systems is required to elucidate the aetiology of such symptoms.

Electrocardiogram was abnormal in 88.4% of the patients which is thought to be an early indicator of cardiomyopathy.^{10,14} Specific changes were common as Ratio of QT/PQ was above normal limits as related to heart rate in most of our patients, which in addition to tall R waves in lead V₁ is suggested as a criteria for preclinical involvement and is termed as 'electrocardiographic myopathic index'.^{11,12} QT interval was prolonged but PQ interval was significantly shortened in these patients which accounts for high QT/PQ ratio. There are many possible contributors to QT prolongation such as hypokalemia, hypomagnesemia, cardiomyopathy, left ventricular hypertrophy, which are often present in the course of DMD and BMD. Similarly it is known that PQ shortening may be due to atrial hypertrophy or atrial fibrosis. Pathological reports suggest that most of these patients have atrial fibrosis rather than hypertrophy.⁹ Again this cardiomyopathic index is increased in carriers also and could be useful clinically as a measure of preclinical cardiac involvement.^{13,26} Q waves in the ECGs of DMD and BMD patients in the inferolateral leads is now termed as pseudo infarction pattern. The aetiology of these Q waves remains unclear. It is thought to be due to myocardial fibrosis. Our study confirms the previous suggestions that Q waves are present in these patients even from the age of six years. Tall R waves in lead V₁ and R/S ratio >1 in the same lead was present in most of the ECGs, which are thought to be a criteria of preclinical involvement in these patients.¹³ These tall R waves in right precordial leads of the ECG of DMD and BMD patients has been variously attributed by different authors to thoracic deformity, including changes in the anteroposterior chest dimension, pulmonary hypertension, conduction defects due to myocardial dystrophy and ventricular hypertrophy. The clinical, pathological, electrocardiographic and haemodynamic evidence for and against these various possibilities has been extensively reviewed,^{14,15} but none of these explanations are entirely satisfactory.

Twenty six out of 52 patients showed P wave abnormalities these might be due to left or right atrial hypertrophy, but these changes did not coincide with atrial enlargement on echocardiography. Similarly some patients had T wave and ST segment changes of uncertain aetiology. Some patients showed U waves which are suggested as normal findings in childhood but these U waves at the age of 16 to 18 years may be compatible with frailty of these patients.

Non-specific changes such as RBBB were present in some of the patients and these reflect damage to interventricular conduction system due to progressive fibrosis which is known to occur in dilated cardiomyopathy. Such fibrotic changes may progress to complete heart block and contribute to sudden death in this condition. As described in results, some patients had ECG evidence of left or right ventricular hypertrophy, but this did not necessarily coincide with echocardiography. This discrepancy would be explained either by the poor quality of echo images or the greater amplitude of ECG recordings obtained in patient with muscular wasting.

Holter monitoring (48-hour tape) may provide additional information about conduction tissue disease but in our study, only a few of the patients showed evidence of any significant abnormality.

Echocardiography was abnormal in 80.7% of patients which ranged from mildly depressed left ventricular function and mild hypokinesia to dilated left ventricle and global hypokinesia. In addition, the severity of left ventricular depression was unrelated to age. It is known that precise echo measurements as systolic and diastolic functions are very useful in evaluating cardiac involvement in these patients. But in our study most of the echoes were of so poor quality that only a crude classification of LV function could be done and detailed measurements were possible only in few of the patients.

Twelve DMD patients were found to have dilated cardiomyopathy but only three were in heart failure. Four patients in Becker group had dilated cardiomyopathy but none had cardiac failure. Due to perhaps limited number of patients studied we could not find any relationship between ages of the patient and progression of cardiomyopathy. Some of the patients had dilated cardiomyopathy at the age of 16 to 18 years in the DMD group and 34 years in the BMD group others had only preclinical involvement at the age of 19 in DMD and 53 in BMD respectively.

As this study was based on an index cardiac assessment at different ages it was not possible to comment on progress of the cardiomyopathy, but some of the patients had previous ECGs which allow more comments. The patients who had clinically evident cardiac involvement in their index assessment at the ages of 15 to 19 years had preclinical ECG changes at the ages of 5 to 8 years (10 to 11 years before) in the DMD group. Similarly in the BMD group 4 patients showed preclinical changes in their ECGs at the ages of 26 and 33 years. Four DMD patients had normal ECGs at the age of 7 and 9 years and had progressed to clinically evident cardiac involvement after 8 to 10 years. Present and 7 year old ECGs of 2 of DMD patients are shown in Figure-2 and 3.

CONCLUSION AND SUGGESTIONS

The logic in undertaking cardiac assessment in asymptomatic patients with Duchenne, Becker and intermediate forms of muscular dystrophy is based on the assumption that cardiac status dictates prognosis for a significant proportion of these patients. The proof that this is so remains lacking. Morbidity and mortality could occur as a result of either left ventricular dysfunction or conduction tissue abnormality. Cardiac assessment therefore is designed to detect preclinical stages of left ventricular dysfunction and check also for the presence of intra-atrial, intra-ventricular or AV conduction abnormalities. Holter recordings are required to identify non-invasively, tendencies to tachyarrhythmias either of intra-atrial re-entry or ventricular re-entry tachycardias.

Routine testing of these patients implies that treatment is available to reduce or reverse cardiomyopathic processes and prevent or suppress arrhythmia tendencies. Detection therefore, of significant left ventricular dysfunction would lead to a recommendation for ACE inhibitor therapy, diuretics and/or beta blockade. The evidence of such treatments would be effective in reversing or delaying the progression of left ventricular dysfunction remains to be established. Similarly patients with advanced conduction tissue disease would be recommended a pace-maker implantation and those with significant tachyarrhythmias would have antiarrhythmic therapy instituted. Whether these treatments would improve prognosis and the degree to which they would be successful in improving symptoms is also unclear.

It is assumed that ACE inhibitor therapy and pace maker implantation for dilated cardiomyopathy and advanced conduction problems would be effective.^{32,33} It is on this basis that routine screening is now advised based on the high incidence of co-existing cardiomyopathies in these patients.

Given the immobility and difficulty in these patients accessing medical services it is important that screening is both sensitive and specific. The results of this retrospective analysis highlight many of the difficulties and assumptions inherent in the routine screening strategy. The minimum screening protocol should involve 12-lead ECG, 48-hour Holter monitoring and echocardiography from the age of 10 yrs.³⁴ It seems reasonable to repeat these assessments at intervals of 1–2 years in patients who have abnormalities identified on their initial index examination. In the absence of symptoms however, progression in the abnormality is probably needed before recommending therapy to prevent the onset of symptoms.

The optimum method of assessing left ventricular function remains unclear. While echocardiography is the simplest technique available, this study shows many of the limitations in its routine

use in this patient group. On the basis of these results it seems that standard trans-thoracic echocardiography is a very crude tool to assess left ventricular function and that radionuclide ventriculography or more invasive echo, such as transoesophageal echo may be warranted. It may be that a more detailed echo assessment requiring a considerable increase in imaging time due to the delays in positioning patients who are highly immobile and frequently wheelchair bound would improve the yield of standard echo.

A combined myocardial perfusion and radionuclide ventriculogram procedure would make the most useful combined assessment in the event that echocardiography proves disappointing.

Signal averaging of the ECG and QT dispersion measurements may provide useful pointers towards ventricular tachyarrhythmias which might ultimately determine prognosis in this patient group but their use remains experimental at present.

It is concluded that cardiomyopathy is prevalent from preclinical to clinically evident stages in DMD, BMD and IMD patients. They should be assessed for their cardiac function routinely and at frequent intervals to improve their management because these patients remain asymptomatic even at a very late stage of cardiac failure.

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