Cardiac Evaluation in a Group of Pediatric Female Carriers of Dystrophinopathy

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ABSTRACT

Objective: To evaluate the cardiac status among a group of female carriers of Duchenne and Becker muscular dystrophy under the age of 16 years and to determine the frequency of cardiac abnormalities.

Methods: Eight female carriers were identified within the register of the Newcastle Muscle Centre (mean age 11.9±4 years; range 5-16). Clinical examination, ECG, 2-dimensional echocardiography and Doppler studies were performed for all cases. This study was conducted during the period between January 2001 till July 2008.

Results: Four (50%) were carriers of Duchenne and four (50%) of Becker muscular dystrophy mutations. All had normal cardiac examination. No one had any of the typical electrocardiographic changes seen in affected males with cardiac dystrophinopathy. No one had echocardiographic changes suggestive of cardiomyopathy. Heart dimensions were normal in all subjects. None had evidence of left ventricular impairment or regional wall motion abnormalities.

Conclusion: Cardiac involvements in female carriers of Duchenne and Becker muscular dystrophy are unlikely to occur in the pediatric age group under the age of 16 years. Cardiac surveillance is justified after the age of 16 years.

Key words: Duchenne muscular dystrophy, Becker muscular dystrophy, Female carriers, Cardiomyopathy

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Introduction

Duchenne (DMD; Online Mendelian Inheritance in Man [OMIM] reference 310200) and Becker (BMD; Online Mendelian Inheritance in Man [OMIM] reference 300376) muscular dystrophy are sex-linked recessive disorders, caused by mutations in the dystrophin gene.[1,2] Dystrophin protein the product of dystrophin gene is associated with dystrophin-glycoprotein complex and not directly inserted in the muscle membrane and contributes to the stability and integrity of muscle membrane protein. In cases where dystrophin is defective this will lead to disruption of the linkage between the extra cellular matrix and the cytoskeleton.[3] The lack of dystrophin in the heart leads to progressive degeneration of the cardiomyocytes, fatty infiltration and fibrosis.[4] The end result is a state of dilated cardiomyopathy passing a stage of hypertrophy.[5] Cardiac involvement is a well recognized complication in adult female carriers of DMD/BMD.[6-8] The degree of cardiac involvement in these carriers varies from asymptomatic to severely affected with dilated cardiomyopathy (DCM) and heart failure, necessitating biventricular pacing or even heart transplantation.[9] Moreover, DCM with severe heart failure could be the only manifestation in these carriers without skeletal muscle weakness.[10,11] There is a paucity of

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information regarding cardiac involvement in female carriers of DMD/BMD in the paediatric age group. Politano *et al*. reported 15% risk of developing cardiac abnormalities in carriers below the age of 16 years.[6] Female carriers of DMD/BMD above the age of 16 years are now offered a routine cardiac evaluation according to guidelines for early detection and treatment, if needed, of abnormal cardiac findings.[12] Giving the fact that adult carriers are at risk of cardiac abnormalities and no clear data regarding those in the childhood age, we evaluated cardiac status in confirmed DMD/BMD female carriers under the age of 16 years.

This study was conducted to evaluate the cardiac status among a group of female carriers of Duchenne and Becker muscular dystrophy under the age of 16 years and to determine the frequency of cardiac abnormalities

Methods

All female carriers of the Xp21 gene mutations known to the Northern regional Muscle Service (Newcastle upon Tyne/UK) were offered cardiac evaluation in the period between January 2001 till July 2008. Inclusion criteria were any female under the age of 16 years with confirmed carrier status by DNA test when a mutation in the dystorphin gene was found or by pedigree analysis. All subjects underwent clinical assessment, including detailed medical history and physical examination, and cardiac evaluation which comprised the following: 12 lead electrocardiogram (ECG), transthoracic echocardiography and Doppler evaluation. These tests had been chosen due to cost effect, availability and being non-invasive.

Creatine phosphokinase (CK)

Serum CK level were offered for all subjects and any reading above 160 IU/L were considered abnormal.

ECG evaluation

Standard 12 lead ECGs were recorded in all subjects. Measurements were then made from three consecutive sinus beats from each of the 12 leads of ECG using a digitizer and associated by computer the method described previously.[13] ECGs were considered abnormal if any of the changes typically seen in affected males with cardiac dystrophinopathy were presented which include sinus tachycardia, pathological Q-waves, repolarisation abnormalities in the infero-lateral or antero-septal leads or abnormally large voltages in the right precordial leads V_1-V_2.[14-16] Pathological Q-wave defined by amplitude more than one third of R wave or more than 0.04 second (40 ms) in the right pre-cordial leads.[17] Abnormal T-waves were determined by discordance between QRS and T wave orientation or the presence of U-waves. Other ECG criteria assessed were conduction abnormalities, bundle branch block or tachyarrhythmia, and QT segment length (QTc, normal<0.45).

Echocardiogram evaluation

All the subjects underwent transthoracic echocardiogram evaluation performed by experienced technicians, measuring the following variables: LVEDd (left ventricular end-diastolic dimension, normal value: 4.0-5.2 cm), LVEDs (left ventricular end-systolic dimension, normal value: 2.3-3.5cm), ejection fraction (EF, normal >60%), inter-ventricular septal thickness as an indicator of hypertrophy (IVS, normal <1.2 mm) and calculated shortening fraction (FS) with Teicholz methods according to the following formula: (LVEDd – LVEDs/ LVEDd: normal value >28%). Any reading out the normal ranges and/or the presence of regional wall motion abnormalities were considered abnormal. Diastolic function was not assessed.

Results

Patients

Of the 105 female carriers who underwent cardiac evaluation, eight carriers under the age of 16 years at time of cardiac assessment were identified. Four carried the Duchenne and four the Becker gene. Six of them the carrier state confirmed by DNA testing while two were considered obligate carrier by family pedigree analysis (case 7 and 8). The mean age of the group was 11.9$\pm$4 years (range 5-16 year). Five were manifesting carrier while three were asymptomatic. Among the manifesting ones, three presented with muscle weakness alone, while muscle weakness was accompanied by Central Nervous System related symptoms (learning difficulties and behavioral abnormalities) in two (Table I).

Creatine phosphokinase (CK)

CK level was elevated in the four subjects measured. The mean level for the group was 2467 $\pm$ 3113 IU/L (range 330- 7000) (Table I).

Table II: Clinical data, CK level and molecular diagnosis

Case ID	Age (years)	Molecular diagnosis	CK level	Clinical picture
1	5	c.9163 +1G>C (splice s. ex 61)	7000	DMD/MC
2	9	Point mut. Ex 53	2005	DMD/MC
3	10	Deletion ex. 45-48	531	BMD/MC
4	10	Del ex 48-52	*	DMD/MC
5	14	Deletion ex. 45-47	330	BMD/MC
6	15.5	Del ex 5-29	*	DMD/NMC
7	15.8	*	*	BMD/NMC
8	16	*	*	BMD/NMC

DMD: Duchenne muscular dystrophy. BMD: Becker muscular dystrophy. MC: manifesting carrier. NMC: non-manifesting carrier. CK: Creatine phosphokinase. *****: Not available

Table II: Summary of ECG findings

Case ID	Age (years)	R in V1	R in V2	iRBBB	Q wave	T wave abn.	QTC
1	5	Normal	Normal	No	No	No	0.39
2	9	Normal	Normal	No	No	No	0.38
3	10	Normal	Normal	No	No	No	0.38
4	10	Normal	Normal	No	No	No	0.44
5	14	Normal	Normal	No	No	No	0.39
6	15.5	Normal	Normal	No	No	No	0.41
7	15.8	Normal	Normal	No	No	No	0.41
8	16	Normal	Normal	No	No	No	0.39

Normal value: R/V1-2: <28 mm (3-8 years), < 19 mm (8-16 years), <7mm (adult). Q wave: <0.04 second or < 1/3 of R wave. R/S: <1.2. iRBBB: incomplete right bundle branch block. QTc: QT interval corrected fro heart rate, normal <0.45. No: not present

Table III: Summary of echocardiogram findings

Case ID	Age (years)	LVEDd (cm)	LVEDs (cm)	FS (%)	EF (%)	IVS (cm)	RWA
1	5	4.3	2.9	32	*	*	No
2	9	4.5	2.7	33	*	*	No
3	10	4.5	2.6	42	60	0.75	No
4	10	3.3	2.3	32	60	0.8	No
5	14	4.6	2.9	37	67	0.7	No
6	15.5	4.5	3.2	29	60	0.8	No
7	15.8	4.7	3.4	28	60	0.86	No
8	16	4.6	3.2	30	60	0.87	No

LVEDd: Left Ventricular End Diastolic dimension. LVEDs: Left Ventricular End Systolic Dimension. FS: Fractional shortening. EF: Ejection Fraction. *: Not available. RWA: Regional wall abnormality.

ECG findings

All the eight subjects had 12 lead ECG. No one showed any abnormalities which are usually seen in affected males. Mean heart rate was 83 $\pm$ 12 beats per minute. No one showed sinus tachycardia apart from one subject which was explained by anxiety being in hospital due to young age.

The maximum R wave amplitude in V1 and V2 was 16mm which is normal for age.[16] No one had pathological Q wave or T wave abnormalities. QTc was normal in all subjects with maximum figure of 0.44. No evidence of conduction abnormalities were detected in any subject (Table II).

Echocardiogram findings

All subjects had echocardiogram. No one had any abnormality suggestive of cardiomyopathy. Heart dimensions were normal in all subjects. Mean for left ventricular end diastolic dimension (LVEDd) and left ventricular end systolic dimension (LVEDs) were 4.4 $\pm$ 0.5 and 2.9 $\pm$ 0.4 cm respectively. Fractional shortening (FS), derived from end-systolic and end-diastolic measurements was normal in all subjects with mean of 33 $\pm$ 5%. Ejection fraction (EF) was normal in the measured six subjects with mean of 61 $\pm$ 3%. No subject showed evidence of hypertrophic cardiomyopathy. Inter-ventricular septal thickness (IVS) measured in six subjects, was normal with mean of 0.8 $\pm$ 0.06cm. Regional wall motion abnormality was not detected in any of the eight subjects (Table III).

Discussion

Cardiac involvement is considered as an important feature in dystrophinopathies which include DMD, BMD, X-linked dilated cardiomyopathy (XLDCM) and female carriers of DMD/BMD, manifested by Q-wave abnormalities, ST-segment depression, regional wall motion abnormalities, DCM and rhythm disturbances in late stages of the disease which necessitating medical intervention ranging from medical treatment of heart failure to even heart transplantation.[18] Stretch induced damage contributes to muscle fatigue and weakness mediated by changes in intracellular calcium, sodium and pH. This mechanism which is involved in normal muscle fibers damage believed to be exaggerated in cases of muscular dystrophies.[19] The limitation of compensatory cardiomyocyte hypertrophy beside progressive loss of cardiomyocyte in DMD/BMD patients contributes to progressive clinical cardiac course in these patients.

The degree of cardiac involvement in female carriers depends on the amount of X-chromosome inactivation according to Lyon hypothesis.[20] Recent data showed that these carriers are at risk of cardiac involvement and cardiomyopathy with variable frequency according to each study.[6-8] These discrepancies are probably explained by differing thresholds for defining 'abnormality' and the particular parameters measured in each test. The only authors who used control group were Grain *et al*. (56 carriers and 35 controls) and his criteria in definition of abnormal cardiac status were closed to that used in our cohort. On the other hand, Nolan *et al* included only carriers less than 16 years of age, also the upper limit for LV wall and septal thickness was 8mm although no subject showed any abnormal figure.

Bushby *et al.* recommended that cardiac screening should be carried out in any female carrier of dystrophinopathy above the age of 16 years as the frequency of developing cardiac abnormalities is very minimum under this age. This is important in timing the screening, keeping in mind the cost effect, raised anxiety and increase psychological stress especially among young carriers.

Grain *et al.* conducted a cross-sectional study to evaluate the cardiac abnormalities in 56 adult DMD/BMD female carriers and 35 controls.[8] ECG and Echo abnormalities were found in 7% and 14% respectively, while 7% had cardiomyopathy. They concluded that although female carriers are at risk of cardiac abnormalities but most of these abnormalities were borderline and did not require intervention. In an another cross-sectional study performed by Hoogerwaard *et al.* to estimate the frequency of cardiac abnormalities in 129 adult female carriers. Frequency of ECG abnormalities was high as 47%, with 36% had typical changes seen in affected males. In addition, 36% found to have echo abnormalities, among them seven (8%) had dilated cardiomyopathy and no one showed evidence of hypertrophic cardiomyopathy. Moreover, a non-significant trend of increasing echo abnormalities with advancing age was found ($P = 0.07$).[7] Politano *et al*. conducted a longitudinal study, assessing cardiac status in 197 DMD/BMD female carriers. They came up with 41% frequency of clinically evident cardiomyopathy in the carriers aged 15-60 years, and increase frequency of dilated cardiomyopathy with advancing age.[6]

All authors agreed that these carriers at risk of cardiac abnormalities. However, information about cardiac abnormalities in paediatric age group is still limited. There are only two published studies by Nolan *et al*. and Politano *et al*. with diverse outcome. Nolan *et al*. studied 23 girls under the age of 16 years with confirmed carrier status of dystrophinopathy to evaluate the frequency of cardiac abnormalities in this particular group of patients.[21] No cardiac abnormalities were detected in any of the studied subjects, which support the recommendations by the guideline regarding cardiac screening in female carriers of dystrophinopathy.[12] On the other hand, Politano *et al*. included 33 carriers under the age of 16 years and reported 15% (5/33) frequency of cardiac involvement in this age group.[6] Among the five with abnormal cardiac test, four had echo changes of hypertrophic cardiomyopathy and one with dilated ardiomyopathy.

In our study, we did not find any cardiac abnormalities. ECGs were normal in all subjects with no evidence of typical cardiac dystrophinopathy seen in affected males. Echo parameters which had been tested all were normal; no one showed any evidence of dilated heart or left ventricular dysfunction (abnormal EF and FS). Moreover, wall motion abnormalities which are considered a reflection of regional scarring and fibrosis, were not found in any candidate. These finding support Nolan *et al*. findings and incontrast to the findings by Politano *et al*. The high figure of abnormal findings by Politano *et al*. can be

explained by threshold of defining abnormality and by using other methods (cardiac scinitigram) other than ECG and echo.

Progressive cardiac dystrophinopathy is part of the disease in affected males. Timing of starting treatment with cardioactive medications is important to delay the progression and to some point improving left ventricular (LV) function. Treatment with angiotensin converting enzyme inhibitors (ACEI) proved to be effective in delaying the deterioration of LV functions and decrease mortality in DMD even in those with normal LV function.[22,23] β-Blockers showed synergistic effect when added to ACEI in DMD patients.[24] This has crucial implication on screening timing for early detection of cardiac abnormalities and starting treatment.

Our study suggests that cardiac abnormalities are unlikely to occur in the carriers under the age of 16 years. This is supported by Nolan's findings, therefore, adherence to the screening guidelines regarding female carriers under the age of 16 years is justified.

Limitations of the Study

The number of patients included in the study was relatively small. A prospective well controlled study recruiting larger number of candidates would be more helpful in confirming these findings.

Conclusion

Cardiac involvements in female carriers of Duchenne and Becker muscular dystrophy are unlikely to occur in the pediatric age group under the age of 16 years. Cardiac surveillance is justified after the age of 16 years.

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