Cardiac assessment in childhood carriers of Duchenne and Becker muscular dystrophies

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Abstract

Cardiac disease in adult female carriers of the X-linked dystrophinopathies, Duchenne and Becker muscular dystrophies, is a well-recognised entity. A single study has reported a 15% incidence of cardiac abnormalities in female carriers under 16 years. Our study aims, clinically and with electrocardiograph and echocardiograph, to determine the incidence of cardiac abnormality in young girls who are proven carriers of X-linked dystrophinopathies. Twenty-three girls aged 6.2–15.9 years were assessed. All had normal cardiac examination. None had electrocardiograph abnormalities consistent with dystrophic cardiomyopathy. Left ventricular fractional shortening ranged from 33 to 55% (normal > 28%). Septal thickness, posterior wall thickness and wall thickness ratio were within normal limits. No cardiac abnormalities have been demonstrated in young girls who are proven carriers of X-linked dystrophinopathies in our study. This has important implications for planning timing of carrier determination and cardiac assessment.

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1. Introduction

Cardiac disease is a recognised complication in adult carriers of the X-linked dystrophinopathies (XLD), Duchenne and Becker muscular dystrophies [1–6]. Myocardial fibrosis and fatty replacement develop in a characteristic fashion and result in hypertrophic and dilated cardiomyopathy. The incidence of cardiac abnormalities in carriers increases with age [1–3]. Little information is available on cardiac involvement in carriers of XLD in the paediatric age group. A single study [2] found that five out of 33 female carriers (15%) under 16 years of age had a cardiac abnormality attributable to XLD. In light of this information and the risk of cardiac involvement in the older age group, we instigated cardiac assessment in confirmed carriers of XLD aged under 16 years. This study aims to assess the incidence of cardiac abnormality in these young girls based on our local population.

2. Patients and methods

The study subjects were consultands of patients with XLD from the Sydney Children’s Hospital Muscle Clinic. Carrier status of female relatives under 16 years was determined either by haplotype studies indicating inheritance of the Xp21 containing the identified dystrophic allele, or by creatine kinase measurement and pedigree assessment. From August 1998 to July 2001 proven carriers from this group were offered screening for cardiac abnormalities.

Inclusion criteria were proven carrier status, informed consent from the family and age less than 16 years at the time of cardiac assessment. Each girl was assessed by clinical examination, 12-lead electrocardiograph (ECG) and echocardiogram (echo). Echo results were acquired with a Sonos 5500 (Phillips Medical Systems) using standard techniques. Study subjects and their families were informed of the assessment results.

Evidence of an anterior QRS pattern was sought on ECG, demonstrated by high R voltage in V1 or V2, maximum R/S ratio in V1 or V2 and/or increased Q voltage in inferior or lateral leads. Other ECG criteria assessed were QT segment length and the presence of conduction abnormalities such as tachyarrhythmia or bundle branch block.
Echo assessment included confirmation of normal anatomy and evaluation for hypertrophic change or evidence of dilated cardiomyopathy. Indicators of hypertrophy included interventricular septal thickness, left ventricular posterior wall thickness in diastole and the ratio of these two measures (>1.5 indicating asymmetric hypertrophy). Left ventricular fractional shortening (LVFS) was used as an indicator of dilated cardiomyopathy, with a value of <28% indicating impaired systolic function. All values were referenced to paediatric ranges [7].

3. Results

3.1. Patients

From our database of families with XLD, 26 girls under 16 years were identified and confirmed as carriers of Duchenne muscular dystrophy (DMD) (n = 21) or Becker muscular dystrophy (BMD) (n = 5). In 20 girls, carrier status was confirmed by DNA analysis. In cases in which DNA analysis was not applicable, four girls with suspected carrier status by pedigree (sibling with XLD) had confirmation by raised creatine kinase, and two girls were considered obligate carriers as they were daughters of fathers with BMD.

All 26 had cardiac assessment between August 1998 and July 2001, but the results from three girls (DMD carrier n = 2, BMD carrier n = 1) were excluded because although ECG and echo were reported as normal, actual values were not available. Of the remaining 23, all had ECG and detailed echocardiograph assessment. Four ECGs were not available for detailed analysis, however, they were reported as normal.

At the time of cardiac assessment, the subjects ranged in age from 6.2 to 15.9 years, with a mean of 11.4 and median of 9.3 years. All were asymptomatic and none of the girls had cardiac abnormalities on clinical examination.

3.2. ECG assessment (Table 1)

None of the 20 girls whose ECGs were studied in detail had abnormalities suggesting an anterior QRS pattern. The greatest R wave amplitude (measured as the highest of V1 or V2) ranged from 3 to 19 mm. In all cases this was within the age-appropriate range (3–8 years: <18 mm in V1, <28 mm in V2; 8–16 years: <16 mm for V1, <22 mm for V2 where 10 mm = 1 mV) [7]. The maximum R/S ratio ranged from

Table 1

Results of ECG and echo assessment

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Highest R amplitude in V2 (mm)</th>
<th>R/S ratio</th>
<th>QTc</th>
<th>LVFS (%)</th>
<th>Septal thickness (mm)</th>
<th>LV wall thickness (mm)</th>
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* *, not available.

1 ECG criteria measured in millimetres where 10 mm = 1 mV; normal range <28 mm (3–8 years), <19 mm (8–16 years).

2 Normal < 1.2.

3 QTc = QT interval corrected for heart rate, normal < 0.45.

4 LV fractional shortening, normal range > 28%.

5 Upper limit normal = 8 mm.
0.22 to 0.94, and again was within the normal range (<1.2) [7]. No cases had an increased Q wave voltage in inferior leads. QT intervals fell within the normal range. No subjects had tachycardia and no conduction abnormalities were found.

3.3. Echocardiogram assessment (Table 1)

All 23 cases had normal anatomic arrangement on cardiac echo. There was no evidence of abnormalities suggesting dilated or hypertrophic cardiomyopathy. Specifically, neither septal thickness nor left ventricular posterior wall thickness measured greater than 8 mm in any child, and the ratio of these measures ranged from 0.7 to 1.3 with a median of 1.0, and the upper limit of normal 1.5 [7]. LVFS indicated normal left ventricular function in all subjects, with measurements above 28% in every child.

4. Discussion

Dystrophin is a protein of very large molecular weight (427 kDa) and is found in skeletal and cardiac muscles as well as the brain and other tissues [8]. It is the product of the dystrophin gene located on Xp21. The known spectrum of X-linked dystrophinopathy now includes not only the well-characterised skeletal myopathies of DMD and BMD, but also isolated cardiac involvement linked to Xp21 (X-linked cardiomyopathy) [8,9], a syndrome with muscle cramps and myoglobinuria [10] and presentations with cognitive dysfunction [11].

Cardiac abnormalities are frequent in boys with DMD. On ECG, the typical features include an anterior QRS pattern, which is thought to reflect myocardial fibrosis that begins in the posterobasal portions of the left ventricle, then the posterior papillary muscle, the interventricular septum and rarely the right ventricle [8,12]. Lengthening of the QT segment and conduction abnormalities such as tachycardia and bundle branch block are associated with the hypertrophic or dilated cardiomyopathy seen in XLD [5,6,13]. Clinically detectable cardiomyopathy does not usually become apparent until after 10 years of age and is reported to affect approximately 50% of boys by 18 years of age [13]. There appears to be a progression through a stage of cardiac hypertrophy to dilated cardiomyopathy [13]. In BMD cardiac involvement follows a similar pattern, often with later onset, although patients may present at an early age with significant cardiomyopathy despite minimal skeletal muscle manifestations [9].

Evidence has emerged that there is a broad spectrum of dystrophin-related cardiac disease in female carriers. In the late 1960s there were reports of ECG abnormalities, with a similar pattern in affected males, in female carriers of XLD [12,14]. Cases have been reported of dilated cardiomyopathy in female carriers of XLD with little or no skeletal muscle manifestation [4,6]. Evidence suggests that the majority of carriers remain asymptomatic of cardiac abnormalities even with evidence of preclinical myocardial damage [2].

The incidence and definition of cardiac abnormalities in carriers of XLD varies between studies. Politano et al. [2] conducted a longitudinal study, with a minimum 3 year follow-up, assessing for cardiac abnormalities in 197 carriers of DMD and BMD. Only a small proportion (8.1%) had any skeletal muscle manifestations of XLD. Their results suggest an incidence of clinically evident cardiomyopathy (hypertrophic or dilated) of 41% in the carriers aged 15–60 years, with 3% demonstrating conduction defects. These results included abnormalities detected in asymptomatic patients on myocardial scintigram.

Other studies report a lower incidence of cardiac involvement. A cross-sectional study by Hoogerwaard et al. [3] was undertaken to assess the frequency of cardiac abnormalities in 129 adult carriers of DMD or BMD, based on ECG and echo criteria. Thirty-six percent had evidence of ECG changes typical of XLD, and 23% had left ventricular dilatation or frank dilated cardiomyopathy on echo. Only five patients had clinical symptoms (4%). Grain et al. [1] performed a cross-sectional study of 56 adult carriers and 35 controls, assessed by clinical examination, ECG and echocardiogram. In their study only eight carriers (14%) had evidence of XLD-associated echocardiogram abnormalities, and only four of them (7%) had cardiomyopathy. Of the carriers, 7% had ECG abnormalities. The incidence of ECG or echo abnormalities in the carrier group overall was 18%, and only one patient was symptomatic.

All studies agree on an increased incidence of cardiac abnormality with advancing age [1–3,5]. However, information on the paediatric age group is limited. The only published work is based on a group of carriers studied by Politano and colleagues in Naples, reported in 1992 [5] and 1996 [2]. The first paper [5] included all female consistants of DMD or BMD patients aged 2–60 years. Carrier status was not confirmed. Of this group there were two out of 40 subjects (5%) aged less than 13 years who were defined as having clinically evident cardiomyopathy. A description of the type of cardiomyopathy (hypertrophic, arrhythmogenic or dilated) was not given.

A further study by this group, described previously [2], included 33 definite carriers aged 5–15 years, some of whom may have been described in the previous report. In this group, based on clinical examination, ECG, echo and myocardial scintigram, five girls (15%) were identified as having myocardial abnormality. Four had hypertrophic changes defined by echocardiographic criteria as in our study. Dilated cardiomyopathy was found in one girl, defined by fulfilling three out of six echocardiograph and myocardial scintigram criteria. The echocardiographic criteria were similar to those used in our study. There is evidence in XLD patients and carriers that echocardiography is a non-invasive diagnostic tool with similar sensitivity to radionuclide angiography techniques in assessing left ventricular systolic function [15].

Cardiomyopathic index (defined as QT/PQs ratio) was not measured in this study. This index has been used as a
predictor of preclinical cardiomyopathy [2,13]. However, previous studies establishing its use [16] were confined to patients over 14 years in whom the index was abnormal in 15% of controls and 60% of DMD patients. The current study aims at demonstrating clinically relevant cardiac abnormality rather than predictive information.

In our study we aimed to establish the incidence of cardiac abnormalities in confirmed female carriers of XLD in our paediatric population. Cardiac assessment was performed using non-invasive screening with clinical examination, ECG and echo. These techniques are accessible and appropriate for screening an asymptomatic population. We did not find any cardiac abnormalities in our study population.

Our study has limitations in that information was collected retrospectively and as a result not all data were complete. However, it is based on clinically relevant parameters in a significant number of carriers. A prospective controlled study in the paediatric age group would obviously be useful to confirm these findings.

In the management of families with XLD, the timing of carrier determination and subsequent investigations of young girls is a sensitive issue. If cardiac abnormalities were proven to be prevalent at a young age, carrier determination and cardiac assessment would have to be initiated early. Our study suggests that clinically relevant cardiac abnormalities are unlikely to occur in the paediatric age group. As a result, cardiac assessment of female carriers of XLD may be delayed until the teenage years.

Acknowledgements

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References