Original Research Article

Cardiac assessment in children with Duchenne Muscular Dystrophy

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Abstract

Background: Duchenne muscular dystrophy (DMD) is the most common X-linked recessive muscular dystrophy affecting 1 in 3,600 boys. DMD is caused by a mutation in the dystrophin gene, which codes for the protein dystrophin. It's absence leads to degeneration of muscle cells.Striated muscles as well as cardiac and respiratory muscles get eventually affected leading to cardiorespiratory failure.**Objectives:** To assess the cardiac functions in the patients with Duchenne muscular dystrophy and to analyse their changes in correlation to their physical ability and muscle function. **Materials and methods**:A cross sectional observational study was conducted on 30 patients genetically proved of DMD. Clinical details,Gower time,creatinine phosphokinase levels, type of genetic mutation and cardiac functions (symptoms, ECG, ECHO) were noted and analysed. **Results:**6.7% were symptomatic for cardiac involvement. 73.3% patient had abnormal ECG.20% had abnormal 2D ECHO. Deep Q (46.7%) and abnormal R/S in V2 (43.3%) were the most frequent electrocardiographic finding. Deep Q wave (p value=0.025) and abnormal R wave in V2 (p value=0.033) was commonly observed in older age group. Echocardiography was abnormal in 36.6% (n=11). There was no correlation between the ECG and 2D Echo findings. **Conclusion**:ECG is better diagnostic test to detect subclinical cardiac involvement. Regular cardiac assessment along with the timed motor tests should be done in clinical follow up.

Keywords: Duchenne muscular dystrophy, ECG, Echocardiography, Cardiac.

Introduction

Duchenne muscular dystrophy(DMD) is an X-linked recessive disorder, affecting around 1 in 3,600 boys. It is the most common muscular dystrophy affecting patients of all races and ethnic groups [1]. DMD is caused by a mutation in the dystrophin gene, located on the X chromosome at locus Xp21.2, which codes for the protein dystrophin. It is a large protein (427 kDa) that is anchoring between the extracellular matrix and the cytoplasmic cytoskeleton of the myocyte. Dystrophin has an important role in stabilizing the cell membrane of both skeletal and cardiac myocytes. Its absence culminates into fragile sarcolemma which in turn leads to muscle cell degeneration [2].The patients present with motor delay, followed by difficulty in running, climbing and later getting up from squatting posture. Most of the patients are wheelchair dependent by 12 years of age. Along with voluntary muscles, it involves cardiac as well as respiratory muscles eventually leading to cardiorespiratory failure resulting in average life expectancy around 25 years.Cardiac involvement is one of the major causes of morbidity and mortality in these patients of progressive muscular dystrophy. So early identification of cardiac involvement and aggressive supportive care may change the natural history of this disease.This study was carried out to assess the cardiac functions in the patients of Duchenne muscular dystrophy and to analyze correlation of cardiac functions to their physical ability. This study will help to determine the timeline in Indian scenario for cardiac functional deterioration thus with further study will help us in deciding the monitoring guidelines.

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Materials and methods

A cross sectional observational study was conducted in neurology department of Bai Jerbai Wadia Hospital for Children over a period of 18 months. 30 patients of DMD were enrolled in the study. This sample size was calculated based on the number of visits of DMD patients in the previous year. The study was approved by the institutional ethics committee and a written informed consent / assent was taken from the parents of the patients / patients included in the study. DMD patients diagnosed on the basis of clinical presentation, elevated serum creatinine phosphokinase levels, genetic analysis or muscle biopsy and EMG, NCV were enrolled. DMD patients with congenital structural abnormality of heart were excluded from the study. Also, patients suffering from any other acute or chronic disease and who are bedridden were excluded.

Clinical data of patients like age at visit (time of enrollment), age at diagnosis, age at onset of weakness, clinical features, developmental history, family history, presence of cardiac symptoms (on direct questioning) were evaluated. Anthropometry including height, arm span, weight and body mass index were noted. Presence or absence of muscle hypertrophy, spine deformity was also noted.

Assessment of muscle function: Muscle power was assessed using the Medical Research Council (MRC) scale. The muscle strength is graded from zero to five as per MRC scale. The power of the weakest range of motion was registered. Timed motor tests typically used in various clinical trials were performed like Gowers' time, 3 stairs time, fixed point (10 meters) walking time.

Investigations: Serum CPK levels and genetic analysis (using MLPA or PCR technique) for all patients were noted.

Electrocardiography:The study group underwent electrocardi-ographic examination on a conventional 12-lead electrocardiogram. The electrocardiograms of all patients were reviewed and following parameters were noted: characteristic of heart rate, R waves, R–S

ratio, PR interval, Q waves, QT interval, QRS complex. The aforementioned ECG parameters were studied and measured manually and compared with published standard age matched normal values [3].

Echocardiography: Their routine Echocardiographic examination was performed by Paediatric cardiologist by conventional transthoracic Doppler echocardiography with the aid of the machine PHILIPS IE 33 was performed. Following parameters were calculated- LVIDd, LVIDs, ejection fraction and shortening fraction. Echocardiographic variables were corrected for body surface area and Z scores were calculated from matched normal values.

Statistical analysis:Demographic data are given as mean with standard deviation (SD). All statistical analyses were performed by use of Statistical Package for Social Sciences (SPSS) version 15.0. Bivariate correlation analyses have been performed employing Pearson's correlation co-efficient. Differences between two groups were analysed by t-tests. Otherwise data were analysed by the non-parametric Mann-Whitney U-test for two independent samples or by the Kruskall Wallis ANOVA-test for more than two samples. Differences in categorical variables were compared by the Chi-square test. All tests were performed at a significance level of 5%.

Results

Most of our patients' age at onset was between 3 to 5 years, with 63.33% (n=19) patients falling in this group. The mean age at onset was 4.5 years (range 2 to 7.5 years). The mean age at diagnosis was 6.85 years $\pm$ 1.33 years (range = 5 to 9.5 years). The mean age of recruitment of patients in our study was 8.23 years (range 6 to 13 years). The duration of illness in our study was very variable i.e. between the range of 1 years to 9 years with the mean being 3.95 years $\pm$ 2.47 years. 33.3% patients (n=10) had a positive family history.

Out of 30, 15 patients (50%) had developmental delay, predominantly motor delay. Out of which only 1/15 patient (3.3 %) had global developmental delay. 13/15 patients (93.3%) had isolated motor delay, while only one patient (3.3 %) had language delay along with motor delay.

The Gowers' time in our study had a wide range from minimum of 3 sec to maximum of 37.3 seconds with a mean of 11.8 seconds $\pm$ 9.84 seconds. We divided the Gowers' time in 4 groups and the distribution was as follows. Majority of patients had Gowers' time less than 10 seconds. 8/30 (26.7%) had Gowers' time between 0 to 5 seconds, 10/30 (33.3%) had the time between 5 to 10 seconds, 4/30 (13.3%) had Gowers' time between 10 to 20 seconds and 5/30 (16.7%) had the time more than 20 seconds. Also, there were 3 patients (10%) who could not get up from the sitting position in whom the Gowers' time was not possible to test.

Table 1: Distribution of genetic analysis

Genetic analysis	Frequency	Percentage
Deletion	28	93.3%
Duplication	2	6.6%

Table 2: Distribution of abnormal ECG findings

ABNORMAL ECG WAVES	Frequency	Percentage
SHORT PR INERVAL	6	20.0%
PROLONGED QRS	8	26.7%
LONG QTc	5	16.7%
DEEP Q WAVE	14	46.7%
R WAVE IN V1	6	20.0%
R/S IN V1	7	23.3%
R WAVE IN V2	11	36.7%
R/S WAVE INV2	13	43.3%
SINUS TACHYCARDIA	2	6.7%

Table 3: Distribution of abnormal echocardiography findings

2D Echo	Frequency	Percentage
LV DYSFUNCTION	1	3.3%
DILATED AORTIC ROOT	1	3.3%
LA/LV DILATATION	9	30.0%
NORMAL HEART	19	63.3%

Discussion

Duchenne muscular dystrophy is characterized by gradually progressive muscular weakness that also affects the respiratory and cardiac muscles leading to substantial morbidity and mortality. Symptoms usually appear before the age of 5 years, the main clinical signs being progressive symmetrical muscle weakness, proximal muscles being affected more than the distal muscles. This results in loss of ambulation before the age of 13 years. Death usually occurs between 15 and 25 years of age [4]. Cardiorespiratory causes are acknowledged as the major reason for death in advanced stage of disease [4]. In our study we assessed the presence and severity cardiac complications in our patients. We also correlated the cardiac complications in our patients with their clinical profile and muscle strength.

In our study, the majority of the patients i.e. 28 out of 30 patients (93.3%) showed deletion mutation. Other mutations seen was duplication in one patient (3.3%).Our results were comparable to the study done by Manjunath et al[5] who found deletions in 79.5% (66/83) and duplications in 7.22% (6/83), while other studies among Asian population differed from our results where duplication rates were considerably higher and to the extent of 27.3% in Korean[6] and 24.7% in Taiwanese patients[7] as compared to deletions.We divided the subjects into 3 groups- single exon deletion, deletion of exons 10-21, and deletion of exons 45-53 to look for their correlation with age at onset, ECG, 2D Echo abnormalities. There was no significant difference between the age of onset of these 3 groups (p value= 0.852). Also, there was no significant correlation seen between genetic mutations, ECG (p value=0.773) and 2D Echo (p value=0.677). No such correlation has been studied previously in literature. So, genetic analysis cannot predict the cardiac involvement of patients with DMD. However, large number of subjects need to be studied to confirm this.

Cardiac involvement of varying degrees depending upon the stage of the disease is frequently seen in DMD, ultimately resulting in the

development of dilated cardiomyopathy [8].Kornberg and Yiu et al (2008) [9] reported that clinically apparent cardiomyopathy is first evident after 10 years of age, affects one-third of patients by the age of 14 years and is present in all patients over 18 years of age. Similar results were seen in a study by Nigro et al,1990[10] that preclinical cardiac involvement is seen in 25% of patients less than six years of age. This suggests an urgent need for multi-centre clinical trials to determine whether treatment of patients with cardiomyopathy, prior to the onset of symptoms, improves prognosis and quality of life [9]. In our study, 19/30 (63.3%) patients had pre-clinical cardiac involvement i.e. these patients were asymptomatic. This was similar to study done by G. Nigro et al had 59% of patients between 6 to 10 years with pre-clinical cardiac involvement [10]. S. Gulati et al [11] and D'Orsogna et al [12] reported signs and symptoms of cardiac dysfunction in 10 % and 22.2 % respectively. This was more than our study as these studies have recruited patients of older age as compared to our study group. In our study, 73.3% (n=22) patients had abnormal ECG, while only 20% (n=6) patients had abnormal 2D echo if z score more than 2 standard deviation were taken into consideration. Thus, ECG was more often abnormal than echocardiography in our study which contradicted the study done by Hoogerwaard et al who found ECG alterations in 47%, echocardiographic alterations in 36% and dilated cardiomyopathy in 18% as this study was done on adults with DMD [13].

Studies conducted by Nigro et al [10] and D'Orsogna et al [12] revealed electrographic alterations in the whole study population. Similarly, our study had completely normal ECG in only 8 patients i.e. 22 patients out of 30 (73.3%) had some form abnormality on ECG. The most common abnormality found on ECG was the abnormal Q wave in lateral leads seen in 46.7 % of patients (14/30 patients) and second common finding was abnormal R/S ratio in lead V2 seen in 43.3% patients (13/30 patients). 6 patients (20 %) had short PR interval, 8 patients (26.7%) had prolonged QRS complex, 5 patients (16.7%) had long QTc interval. Abnormal R wave in V1 (20%), and V2 (36.7%), and large R/S ratio in V1 (23.3%) were also seen. Sinus tachycardia was seen as an additional finding in 2 patients (6.7%). S. Gulati et al detected ECG abnormalities in 93% of patients which was higher as compared to our study. The commonest abnormalities included R>4 mm in V1 in 93.3%, followed by R/S > 1 in V1 and sinus tachycardia in 76.6% each [11]. Study by Auxiliadora et al reported no differences were found between the groups of normal and abnormal findings in relation to age [14]. When we correlated ECG waves with age at visit, there was significant difference in the age of patients with respect to abnormal Q wave (p value=0.025) and abnormal R wave in lead V2 (p value=0.033). Q wave and R wave in lead V2 were more abnormal in older age. However, no similar correlation was seen for other ECG waves.

Echocardiography allows qualitative assessment of the contractility of the heart and its early diagnosis and treatment. Echocardiography was completely normal in 19 patients (63.3%) in our study. On qualitative assessment, 9 patients (30%) patients had mild LA/LV dilatation, 1 had left ventricular dysfunction, and 1 had aortic root dilatation. We used the Z scores of LVIDd and LVIDs for comparison purpose.

Ejection fraction between 56% to 78% was considered normal in our study [3]. The mean ejection fraction was 62.84% $\pm$ 4.66% which was similar to mean of the previous literature done by Orsogna et al [12] and S. Gulati et al[11]. Whereas in the study ofKall C et al [15] the mean ejection fraction was 43.75, this difference can be explained by the different range of age of patients (7 to 23 years) in this study. The mean shortening fraction (FS) in our study was 33.32% $\pm$ 3.63% whereas FS between 28% to 44% was considered as normal range [3].Only 1 patient (3.3%) had ejection fraction below 56% and FS below 28% in our study. This was supported by a study by Ahuja et al [16] who found lesser abnormalities of FS (14.8%) in their patients. Our study had 3/30 (10%) patients with both LVIDd and LVIDs abnormal, while two patients (6.7%) with abnormal LVIDd z scores and one patients (13.3%) with abnormal LVIDs z scores. S. Gulati et al recorded 64.2% patients with left ventricular ejection fraction <55% and 17.8% of patients with left ventricular ejection fraction <50% [11] which was not a common finding in our patients.

When the correlation ECG and 2D echo findings was studied, there was no statistically significant correlation between the two modalities of cardiac assessment. There was no significant difference in duration of illness (years) between the patients with normal and abnormal ECG waves. Also, the duration of illness was not statistically different between patients with normal and abnormal z-scores of LVIDd (p value= 0.649) and LVIDs (p value= 0.576). The age at enrollment was not different between the patients with normal and abnormal z-scores of LVIDd (p value=0.695) and z-scores of LVIDs (p value= 0.336). Also, ejection fraction and shortening fraction did not have any correlation with the age of the patient in years. M. Kohler at al also had similar results in his study [17].

We performed quantitative tests to determine the muscle strength like the time to climb stairs, Gowers' time, time to walk a distance of 10 meter.

Also, the cardiac parameters like the Z scores of LVIDd and LVIDs were correlated with the following parameters – 3 stairs time, fixed point walking time, Gowers' time and the single breath count. The Gowers' time (p value=0.669 for LVIDd, p value=0.865 for LVIDs) and 3 stairs time (p value= 0.460 for LVIDd, p value=0.729 for LVIDs) had no correlation of statistical significance with the z-scores. Fixed point walking time had a positive correlation (p value=0.024) with the z-scores of LVIDd. This concludes that increasing Gowers' time and 3 stairs time is not parallel with the cardiac dysfunction in DMD. Whereas, increasing fixed point walking time can indicate the need for cardiac evaluation.

Conclusion

Duchenne muscular dystrophy is a progressive muscular dystrophy in which the patients have inevitable silent cardiac involvement usually go unnoticed unless objective tests are applied. . ECG is cheap, easily available and better diagnostic test to detect subclinical cardiac involvement but requires expertise to interpret. Thus, a standard documentation chart including all the ECG abnormalities should be devised for bedside application for early identification of cardiac involvement in these patients.

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Abbreviations

DMD (Duchenne Muscular Dystrophy), 2D ECHO (2 dimensional echocardiography), ECG (electrocardiograph), LVIDd (Left ventricular internal diameter in diastole), LVIDs (Left ventricular internal diameter in systole), LA (Left atrium), LV (left ventricle),

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