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Elham Abdelghafar¹, Amir A. Nawar³, Elwan S.A.¹, Issa H.A.²
Departments of Pediatrics¹, Clinical Pathology³, Benha University;
Neurology², Al-Azhar University; Egypt

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Early Detection of Cardiac Affection in Duchenne Muscular Dystrophy by Cardiac Troponin I & CK-MB

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Departments of Pediatrics¹, Clinical Pathology³, Benha University;
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ABSTRACT

Background: Duchenne Muscular Dystrophy (DMD) is a common genetic disease, early diagnosis of dilated cardiomyopathy (DCM) in DMD enables the start of effective treatment. Myocardial markers such as MB type of creatine kinase (CK-MB) and cardiac troponins are expected to evaluate active myocardial degeneration. However, their availabilities in these patients have not been examined yet. **Objective:** Evaluation of the clinical usefulness of cardiac troponin I and CK-MB in early detection of cardiac affection in patients with Duchenne Muscular Dystrophy. **Subjects and Methods:** This prospective study was conducted in the period from March 2009 to June 2011 on patients with DMD who attended the neuropaediatric clinic of Benha university hospital. Fifty Egyptian males' participative in the study; their ages ranged 4-18 years. The participants were divided into two groups: Group (I) 30 male patients with DMD and group (II) 20 normal male participants matched for age and sex with patients as control. After review of medical records, DMD patients were subjected to thorough history, physical examination, all patients were assessed for motor impairments using Swine-yard-Deaver criteria and then classified into one of five degrees according to the severity of motor disability. Cardiac investigations included chest x ray and echocardiography. Serum levels of Cardiac troponin I, total (CK) and CK-MB fraction activity were measured and statistical analysis was done. **Results:** Mean age of patients was 8.89 ± 2.87 years. Assessment of the degree of motor disability in group I revealed that 10(33.3%) patients had the ability of walking, 13(43.4%) patients were rowing wheelchair and 7(23.3%) patients can sit without support. Estimation of serum levels of CK, cardiac troponin I and CK-MB showed highly statistically significant ($P < 0.001$) increase in group I than in group II. Patients with the ability of rowing wheelchair presented extremely significantly higher values ($p < 0.0001$) in cTnI than patients with other motor dysfunction. CK-MB was highly significantly positively correlated with CK ($r = 0.58$ & p value < 0.001) while cTnI presented non significant correlation with CK ($r = 0.23$). There was significant ($p < 0.05$) negative correlations between LVEF & both cTnI and CK-MB as $r = (-0.38)$ and (-0.407) respectively. **Conclusion:** cTnI & CK-MB are significantly elevated in patients with DMD without obvious cardiac abnormalities. So, they could be useful markers for early detection of cardiomyopathy in DMD patients that enable us to improve clinical intervention in these patients. [Int. J. Ch. Neuropsychiatry, 2012, 9(1 & 2): 163-169]

Key Words: cardiomyopathy, cardiac troponin I, Duchene muscular dystrophy, CK-MB

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common and severe form of muscular dystrophy, occurs in 1 in 3500 male births, caused by mutations within the dystrophin gene, located on the X chromosome and is inherited as an X-linked recessive condition¹.

Cardiomyopathies and arrhythmias are common manifestations of DMD in children². They are first evident on ECG and echocardiography after 10 years of age³. Clinical studies demonstrated a beneficial effect of ACE inhibitors on onset and progression of ventricular dysfunction and survival⁴. ACE inhibition also improved skeletal muscle regeneration in the mdx mouse model for

DMD⁵. Because main medicinal virtue of these drugs is cardio protection, they are considered to be initiated in early stage of cardiac degeneration. However, it is very difficult to detect such condition especially in these patients. Left ventricular ejection fraction (LVEF) measured by ultrasonic echocardiography (UCG) is a standard cardiac index; however, it can not reveal dystrophic process of myocardium directly. Motor dysfunction and respiratory management greatly reduces the load on heart, so that it frequently keeps normal level even in advanced stage of cardiomyopathy⁶. Still more, quantitative measurement by UCG is frequently difficult due to spinal and thoracic deformity. Thus, we can't initiate interventions based on this parameter. Magnetic resonance imaging for diagnosis of cardiac affection in DMD is a powerful tool⁷; however, we cannot apply it in all facilities. Thus, it is quite necessary to know which battery or serological indexes can reveal cardiac condition accurately. There are several serological myocardial indexes, including MB isoform of creatine kinase (CK-MB), and cardiac troponins. They are usually utilized as biochemical indicators of ischemic heart diseases. In addition to their advantages over imaging techniques in terms of cost and feasibility, they have been shown to have superior diagnostic accuracy than echocardiography from the asymptomatic or paucisymptomatic phases of heart failure⁸. However, there have been few assessments of these markers in patients with DMD.

Objective: Evaluation of the clinical usefulness of cardiac troponin I and CK-MB in early detection of cardiac affection in patients with Duchenne Muscular Dystrophy.

SUBJECTS AND METHODS

This prospective study was conducted in the period from March 2009 to June 2011 on patients with DMD who attended the neuropsychiatric clinic of Benha university hospital after getting informed consents from their parents. Children younger than 4 years, those with congenital heart disease, rheumatic heart disease, congestive heart failure, chronic renal failure and or sepsis were excluded

from the study. The diagnostic criteria for DMD were history of proximal muscle weakness in early childhood, objective signs of girdle weakness, calf pseudo hypertrophy and elevated serum CK level. Confirmation of diagnosis was done by electromyography (EMG) and muscle biopsy.

The clinical profile included the age at onset of illness with DMD, Family history of similar illness especially in maternal uncles and sibs, details of motor disability and history of respiratory complaints. Cardiac symptomatology was recorded including history of dyspnea, palpitations, exertional fatigue, paroxysmal nocturnal dyspnea and orthopnea. Systemic examination with special reference to cardiovascular system was done. All patients were assessed for motor impairments using Swine-yard-Deaver criteria and then classified into one of five degrees according to the severity of motor disability as having ability of walking, rowing wheelchair, sitting without support, sitting with reclining and bed-ridden⁹. Cardiac investigations included chest X-ray for cardiomegaly, X-ray spine for kyphoscoliosis and echocardiography. Serum levels of Cardiac troponin I was measured by FIA test from (I-Chroma). Creatine kinase (CK) and CK-MB fraction activity were measured spectrophotometrically by kits from (Human diagnostic), Germany.

Statistical Analysis:

Data were checked and analyzed by using SPSS version 16. Data were expressed as mean \pm standard deviation, numbers and percentages for quantitative variables. Student t-test, Paired t-test, ANOVA and Chi Square(X^2) were used when appropriate. Pearson's correlations were used to assess correlation among each marker. Mann-Whitney's U test was applied to investigate correlation between myocardial markers and motor function. P value < 0.05 was considered to be statistically significant.

RESULTS

Our prospective study included 30 male patients with DMD as group I, their ages ranged from

4-18 years with mean age of 8.89 ± 2.87 years and included also 20 normal male children matched for age and sex (group II) as control. The mean age of onset of the disease was 5.21 ± 2.67 years. Cardiac symptomatology was recorded and shows no history of dyspnea, orthopnea, exertional fatigue, palpitations or paroxysmal nocturnal dyspnea. Clinical examination to chest & heart was done and reveals no abnormalities. Cardiac investigations in the form of chest X-ray for group I was normal (no cardiomegaly). Comparison between echocardiography parameters in both studied groups showed no statistically significant ($p > 0.05$) difference regarding LVESD (left ventricular ejection systolic diameter) & LVEDD (left ventricular ejection diastolic diameter) but there was highly statistically significant ($p < 0.001$) difference between group I and group II regarding LVEF as shown in table (1) although the LVEF in group I was within the normal range.

Assessment of the degree of motor disability in group I showed that 10(33.3%) patients had the ability of walking, 13(43.4%) patients were rowing wheelchair and 7(23.3%) patients can sit without support. Estimation of serum levels of total CK, cardiac troponin I and CK-MB showed highly statistically significant ($P < 0.001$) increase in group I than in group II as shown in table (2). Patients with the ability of rowing wheelchair presented extremely significantly higher values ($p < 0.0001$) in cTnI than patients with other motor dysfunction as shown in Table (3) & Figure (1). CK-MB was highly significantly associated with CK ($r = 0.58$ & p value < 0.001) while cTnI presented non significant correlation with CK ($r = 0.23$) as shown in figures (2) and (3) respectively. There was significant ($p < 0.05$) negative correlations $r = (-0.38)$ and $r = (-0.407)$ between LVEF & both cTnI and CK-MB as shown in figures 4&5 respectively.

Table 1. Echocardiography parameters in both studied groups.

| | Group I (N = 30) | Group II (N = 20) | t | p |
|------------------|---------------------|----------------------|------|---------|
| LVEF (%) | | | | |
| $\bar{X} \pm SD$ | 71.9 \pm 5.0 | 78.2 \pm 2.67 | 5.12 | <0.001* |
| Range | 61-80 | 70-81 | | |
| LVEDD (cm) | | | | |
| $\bar{X} \pm SD$ | 3.85 \pm 0.43 | 3.72 \pm 0.61 | 0.86 | 0.39 |
| LVESD (cm) | | | | |
| $\bar{X} \pm SD$ | 2.51 \pm 0.25 | 2.52 \pm 0.36 | 0.11 | 0.9 |

* Highly significant

Table 2. Cardiac troponin I, total CK and CK-MB levels in both studied groups.

| | Group I (N = 30) | Group II (N = 20) | t | p |
|--------------------|------------------------|----------------------|-------|------------|
| Total CK (U/L) | | | | |
| $\bar{X} \pm SD$ | 9520.000 \pm 4022.12 | 51.0 \pm 32.4 | 10.4 | < 0.0001** |
| Troponin I (ng/ml) | | | | |
| $\bar{X} \pm SD$ | 0.032 \pm 0.008 | 0.022 \pm 0.012 | 3.45 | < 0.0011* |
| CK MB (U/L) | | | | |
| $\bar{X} \pm SD$ | 34.5 \pm 44 | 8.5 \pm 4.66 | 10.58 | < 0.001* |

* Highly significant

** extremely significant

Table 3. Relation between the degree of motor disability and cardiac troponin I in group (I).

| Degree of motor disability | cardiac troponin I (ng/ml) $\bar{X} \pm SD$ | P Value |
|----------------------------|--|--------------|
| Gait (ability of walking) | 0.015 \pm 0.0040 | F = 36.3 |
| Rowing wheelchair | 0.036 \pm 0.0035 | P < 0.0001** |
| Sitting without support | 0.021 \pm 0.0047 | |

** = Extremely significant

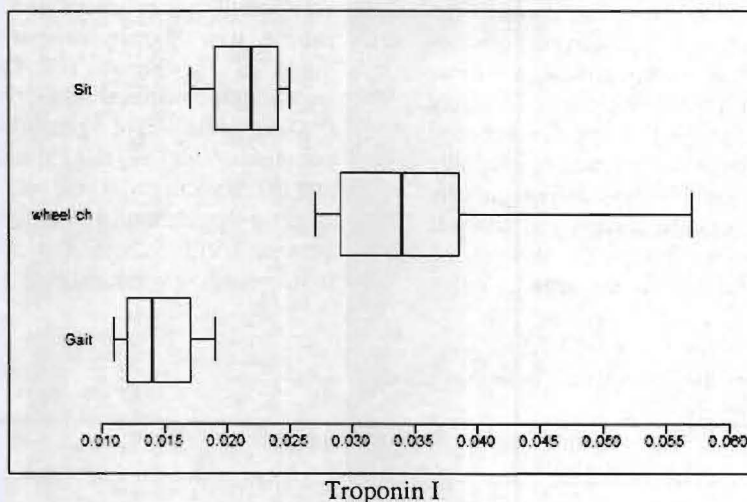


Figure 1. Cardiac troponin I in relation to the degree of motor disability in DMD patients

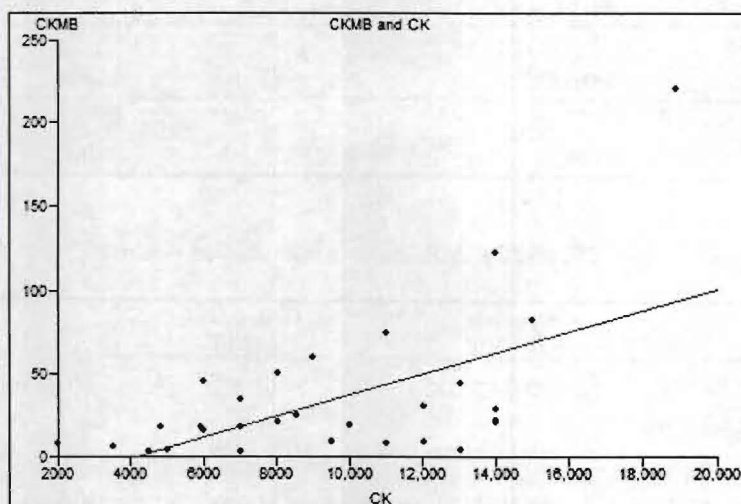


Figure 2. High significant positive correlation between total CK& CKMB in patients with DMD

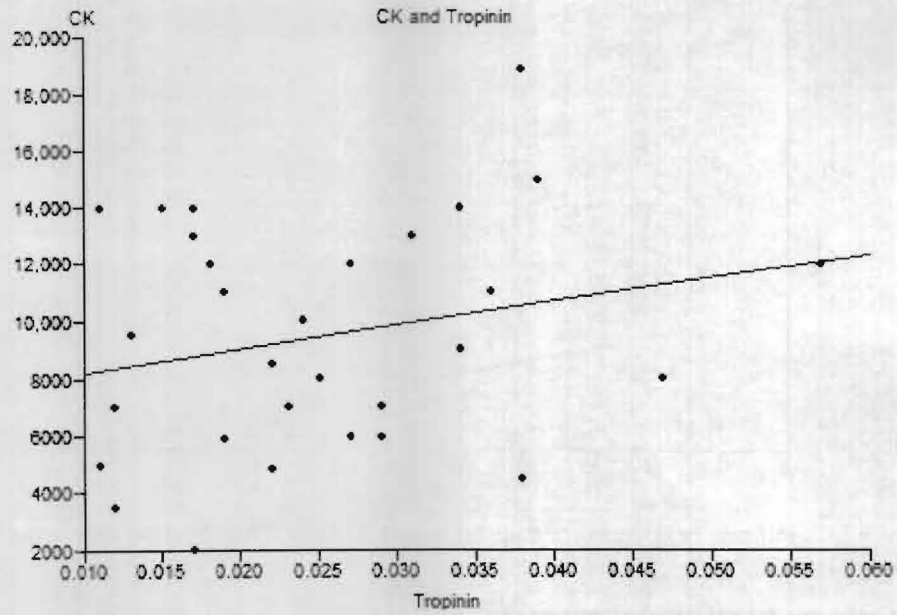


Figure 3. Non significant correlation between total CK & troponin I in patients with DMD.

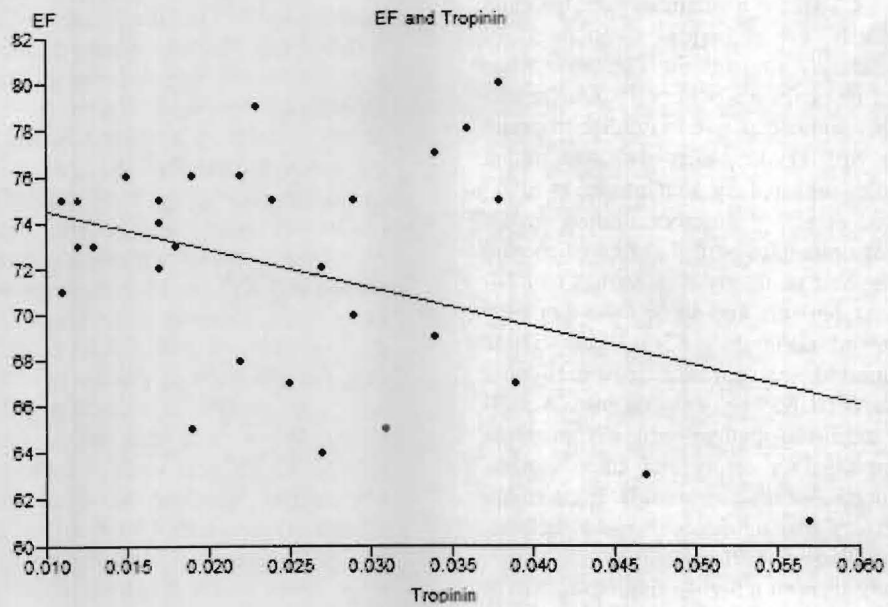


Figure 4. Significant negative correlation between LVEF & troponin I in patients with DMD.

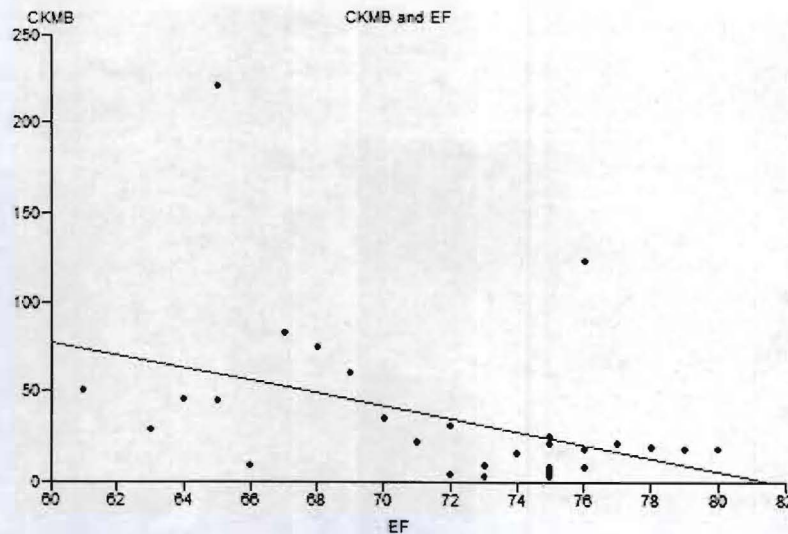


Figure 5. Significant negative correlation between CKMB and LVEF in patients with DMD.

DISCUSSION

CK-MB is a cytoplasmic component of myocardium. CTnI is a member of troponin complex, which is a major component of myofibrils. They appear in serum when destruction of myocardium occurs⁽¹⁰⁾. Our results revealed highly significant rise in cardiac troponin I in patients with DMD which are concomitant with the results reported by Matsumura et al⁽¹¹⁾ and Schoeffler et al⁽¹²⁾. Another finding in our study was that patients with the ability of rowing wheelchair showed relatively high values of cTnI while ambulant patients and those who can only sit alone showed rather low cTnI levels. These findings suggested that cardiac degeneration is activated from certain stage of the disease. Also, it seemed that cardiomyopathy frequently progress insidiously in DMD patients and since cardiac load is reduced greatly by motor impairment and/or respiratory managements in these patients, the sensitivity of stress markers decline¹³.

Our study showed a highly significant rise in CK-MB levels in DMD patients. These results are concomitant with the studies of Hsiao et al.¹⁴ and

Matsumura et al.¹¹. Actually, in our study CK-MB showed significant positive correlation to CK, while cTnI showed poor correlation to CK. It is known that cross reaction can occur among CK isoenzymes¹⁵. On the contrary, it had been certified that cTnI is uniquely expressed in cardiac muscle and is not expressed in other tissues through all developmental stages¹⁶. The absence of any correlation between CK and cTnI found in our study proved that the specificity of cTnI as cardiac marker is high even in DMD patients. Our results revealed that cTnI was negatively correlated to LVEF which go with the findings of Hyeon and Ki¹⁷, as they reported that, cTnI level differed significantly according to left ventricular ejection fraction and Takao et al.¹⁸, who found that; the elevation of plasma cTnI was associated with LV systolic dysfunction in patients with DMD. We noticed that the correlation between cTnI & LVEF was weak correlation ($r = -0.38$). Myocardial markers as cTnI reflect cardiac degeneration, while LVEF reflect cardiac stress. In DMD patients, CK is higher in early disease stage when motor function is still preserved and dystrophic process is active. Then it decreases in advanced stage when muscle atrophy and motor

impairment progressed severely. Same way, myocardial destruction is suspected to precede cardiac dysfunction¹³.

Anyway, when active cardiac destruction is suggested by the elevation of cTnI & CK-MB, we have enough reasons to start cardioprotective therapy and assess the effect of therapy. In ambulant patients, hypotensive action by ACEI and beta-blockers can be serious problem. It is not clear whether initiating cardioprotective therapy from initial disease stage can prolong the onset of cardiac degeneration. To answer this question for preventive therapy we need more studies.

Conclusion

CTnI & CK-MB values are significantly elevated in patients with DMD without obvious cardiac abnormalities. So, they could be useful markers for early detection of cardiomyopathy in DMD patients that enable us to improve clinical intervention in these patients.

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