

Myocardial Injury in Scorpion Envenomed Children: Significance of Assessment of Serum Troponin I and Interleukin-8

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Abstract

OBJECTIVES: (1) To investigate the significance of assessment of serum levels of cardiac troponin I (cTnI) and interleukin-8 (IL-8) beside other biomarkers of myocardial injury in scorpion envenomed children. (2) To find the correlation between these biochemical indices with clinical status, prognosis and outcome of these cases. **METHODS:** Forty-one children in Upper Egypt were admitted to Pediatric Intensive Care Unit, Assiut University Hospital, for scorpion envenomation. They were compared with fifteen apparently healthy children of matching age as controls. The victims and controls were subjected to complete clinical examination, full blood count and arterial blood gases analysis. According to severity of scorpion envenomation, 17 children had manifestations of severe envenomation and clinical signs of toxic myocarditis (severe cases), 14 children had moderate manifestations of envenomation without clinical evidence of carditis (moderate cases) and 10 cases showing only mild symptoms of envenomation (mild cases). The serum levels of cTnI and IL-8 beside the enzymatic activities of creatine phosphokinase (CPK), CPK-MB isoenzyme (CPK-MB) and lactate dehydrogenase (LDH) were determined once for mild cases and controls on admission and twice for severe and moderate cases on admission and after 24 hrs. The measurements of electrocardiography (ECG), echocardiographic measurement of % fractional shortening of left ventricle (%SF), left ventricular ejection fraction (LVEF) and cardiac chambers dilatation were done for severe and moderate cases. **RESULTS:** All the envenomed victims showed significantly higher mean values of CPK, CPK-MB, LDH, and IL-8 on admission in comparison to control group. cTnI was not detectable in the sera of control group as well as patients with mild envenomation. The mean values of CPK, CPK-MB, LDH, and IL-8 were significantly higher in severe cases while only IL-8 and CPK-MB were significantly higher in moderate cases in comparison with mild cases. The mean values of IL-8, cTnI, CPK, CPK-MB and LDH were significantly higher in severe cases both on admission and on follow-up comparing with moderate cases. The case fatality rate was 12.5% and all were from severe cases with toxic myocarditis (5/41 = 12.5%). The non-survivors victims showed significant higher mean values of only cTnI on admission and both cTnI and IL-8 on follow up in comparison to the survivors. Significant reduction of % SF and LVEF were noticed among the non-survivors in comparison to survivors. The cTnI showed 100% specificity and sensitivity for diagnosis of myocardial injury in relation to Echo finding in the envenomed victims. In severe cases, cTnI was positively correlated with IL-8 while negatively correlated with %SF and LVEF. **CONCLUSION:** it may be suggested that cTnI is the most specific marker for diagnosis of myocardial injury in scorpion envenomation, which is almost associated with skeletal muscle injury. Other biochemical markers did not show such specificity. Also, IL-8 may be involved in the pathogenesis of myocardial injury of scorpion envenomation. Both cTnI and IL-8 may be useful to forecast the fatal outcome in scorpion envenomation.

Introduction

Scorpion envenomation is a common medical problem and life-threatening hazard in many countries. Scorpion envenomation in children can be a potentially fatal condition. Neurotoxins and cardiotoxins are present in the majority of scorpion venoms [1]. The signs and symptoms of envenomation are usually more severe in children especially younger ones [2–3]. Scorpion envenoming results in multi-organ system failure and death. It is brought about by a massive release of catecholamines, glucagon and angiotensin II and a simultaneous reduction in insulin levels [4–5]. The severity of envenomation is related to neurological and cardio-respiratory dysfunction. The mechanism of scorpion envenomation induced cardiac dysfunction is still unclear [6]. Gueron et al., [7] hypothesized that catecholamine storm post envenomation may cause cardiac dysfunction by catecholamine-induced hypoxia and that death might result from myocarditis and congestive heart failure [8]. Some authors suggested that cardiac dysfunction in scorpion envenomation may be due to a direct effect of scorpion venom evoking the so-called *scorpionic myocarditis* characterized by non-specific ultra-structural changes [9]. Nouira et al. [10] showed the presence of right and left ventricular dysfunction after scorpion envenomation providing further augmentation to the hypothesis of *scorpionic myocarditis*.

Myocardial damage in children may be clinically occult in a variety of stressful conditions. However, biochemical markers have not been routinely used in children at risk of myocardial damage due to lack of sufficient specificity. As the criterion for myocyte injury is not well established, so the need for a specific serum marker for myocardial injury might be useful to augment the clinical and echocardiographic (Echo) diagnosis of myocarditis [11]. Troponin I, C and T form a complex that regulates the Ca²⁺ mediated interaction of actin and myosin in striated muscles. Troponin I from the cardiac muscle and slow and fast twitch skeletal muscles are products of different genes with unique amino acid sequence. The developed monoclonal antibodies to cardiac troponin I (cTnI) have non cross reactivity with the skeletal muscle form were reported [12]. Briassoulis et al., [13] proved that cTnI is an early marker of viral myocarditis. Adams et al., [14] stated that the increases in cTnI don't occur despite severe acute or chronic muscle injury even when level of creatine phosphokinase (CPK) and CPK-MB isoenzyme (CPK-MB) are increased unless cardiac injury is present.

Scorpion venoms can stimulate the neuroendocrinal-immunological axis by its ability to release catecholamines, corticosteroids, bradykinin and prostaglandins and all these agents proved to induce the release of immunological mediators as cytokines [15]. Cytokines regulate and amplify the immune response, induce tissue injury and mediate complications of the

inflammatory response [16]. There is now accumulating evidence to suggest a causal relationship between overproduction of certain cytokines such as interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) and both morbidity and mortality associated with critically ill patients [17]. Studies from Egypt indicated that levels of cytokines in scorpion envenomed children correlated with the clinical severity of envenomation [3].

Interleukin-8 (IL-8) is a potent chemoattractant factor for neutrophils, basophils and T lymphocytes and to control their trafficking [18]. Endothelial cells have been shown to produce IL-8 on stimulation with a variety of inflammatory mediators. Moreover, cultured endothelial cells release IL-8 under hypoxic conditions (Karakurum et al., 1994). According to the current knowledge, cytotoxic lymphocytes rather than monocytes are found at sites of myocardial inflammation. The inflammatory cytokines are target to myocardial cells as the immune cells adhere to myocytes (Lang and Schreiner, 1994).

The aim of the present study was to assess the frequency of myocardial injury in scorpion envenomed children using the different biochemical markers (cTnI, IL-8, CPK, CPK-MB and LDH) hoping to identify the most specific marker for early detection of myocardial damage and forecasting the prognosis of these cases. In addition, to clarify the role of IL-8 in the pathogenesis of myocardial injury in scorpion envenomation and also to find the correlation between these biochemical indices with clinical status.

Materials and Methods

The present study included forty one children admitted to the Pediatric Intensive Care Unit (ICU) in Assiut University Hospital during the summer months of 2001. The mean age of the victims was (Mean \pm SE) 7.3 \pm 0.72 years. They were 26 males and 15 females. Another fifteen apparently healthy children of matchable age and sex considered as controls. The patients were classified into 3 groups according to the severity of envenomation: **Group (1) (severe cases)** includes 17 victims showing manifestations of severe envenomation such as encephalopathy, pulmonary edema, seizures and clinical suggestive of myocarditis e.g. heart failure, cyanosis, cardiogenic shock, dysrhythmia (SV-T, ventricular ectopic), muffled 1st heart sound, apical pan-systolic murmur and ECG changes (prolonged QTc interval, various degrees of heart block, low voltage, ventricular ectopics). **Group (2) (moderate cases)** consisted of 14 cases showing signs of moderate envenomation such as bronchospasm, vomiting, abdominal distension, seizures and/or encephalopathy hypo- or hypertension, tachy or bradycardia but without clinical evidence of carditis. **Group (3) (mild cases)** contained 10 cases showing manifestations of mild envenomation e.g. local pain, lacrimation, salivation, priapism and vomiting. All patients and controls were assessed by history and clinical examination with exclusion of those

with chronic heart, renal or hepatic disorders. Also a complete blood count and the arterial blood gases for each victim were done.

The blood samples were taken from each victim, only one sample from the controls and mild cases and twice for severe and moderate cases. The first sample was on arrival and the second sample was after 24 hours. The blood sample was drawn by venipuncture and the serum sample was stored at -20°C until biochemical parameters were determined. Serum enzyme activities of CPK, CPK-MB and LDH, and serum levels of cTnI and IL-8 were determined. Echo examinations for all the patients of severe and moderate envenomation were done for measuring % shortening fractions of left ventricle (%SF) and left ventricular ejection fraction (LVEF) and the presence of chamber dilatation. Informed consents were taken in this study from families of victims and controls.

Biochemical analysis

Serum LDH activities were estimated using UV-kinetic kit (Procedure No. 0940, Stanbio Lab, Inc., USA). Serum CPK was estimated using UV-kinetic Kit (Procedure No.0910, Stanbio. Lab., Inc., USA). Serum CPK-MB activity was determined by the immunoinhibition method using commercial kit (Cat No. 81779, Diagnostics, Italy). Serum cTnI level was determined using Immulite troponin I kit which is a solid-phase, two-site chemiluminescent enzyme immuno-metric assay for use with the Immulite Automated Analyzer (Cat No. LKTI, Diagn. Products Corp, USA). The detection limit of cTnI assay was approximately 0.1 ng/ml. Serum level of IL-8 was measured using ELISA Kit (Cat. No. KAC 1301, Biosource Europe, S.A, Belgium). The sensitivity of the IL-8 assay was 0.7 pg/ml.

Statistical analysis

Results were expressed as mean \pm SE. The statistical significance of differences between groups was analyzed by a Students t-test. Data were considered statistically significant if P-values were <0.05 . Linear regression was used to assess correlation between the parameters.

Results

Our results are shown in Tables 1–4 and Figures 1–4. Out of the studied victims, 63.4% were male children. The percentage frequency of the various clinical manifestations, ECG, and Echo variables among the severe and moderate cases is represented in Table 1. All patients with severe envenomation showed manifestation of multiple organ failure. The age range of the victims was 7–14 years. The mean time interval between the occurrence of the sting and admission was 15.9 ± 1.22 hours. The foot was the mean site of sting in 60.9% of victims while 24.3% of victims were stung in the fingers, 9.7% in the upper arms and 4.8% were stung in the upper chest. Neither the sex, nor the time

interval between the sting and admission had any effect on the clinical manifestations or the outcome of the patients. The case fatality rate of the victims was 12.5% (5/41), all of them were from severe cases and 3 of them were mechanically ventilated.

The mean values of IL-8, CPK, CPK-MB and LDH in all patients were significantly higher than controls. cTnI was not detectable in the sera of the control group as well as in mild cases. In comparison with mild cases on admission, the mean values of IL-8, CPK, CPK-MB and LDH were significantly higher in severe cases while only IL-8 and CPK-MB were significantly higher in moderate cases. Moreover, the levels of IL-8, CPK and CPK-MB were significantly higher in mild cases than controls (Table 2). In severe cases, the mean values of IL-8, cTnI, CPK, CPK-MB and LDH were significantly higher in either on admission or on follow-up comparing with moderate cases (Table 3). The non-survivors victims showed significant higher mean values of only cTnI on admission and cTnI and IL-8 beside CPK, CPK-MB and LDH on follow up in comparison to the survivors (Table 4). The non survivors showed significant reduction in the % SF (27.8 ± 0.82) in comparison to the survivors (30.6 ± 0.75 , $P < 0.05$). Meanwhile, the non survivors showed significant lower value of LVEF (23.7 ± 1.92) in comparison to the survivors (38.4 ± 1.93 , $P < 0.025$). The cut-off value of serum level of cTnI (ng/ml) in severe and moderate cases was shown in Fig. (1). The cut-off value of cTnI in severe cases was found to be >1 ng/ml. The cTnI showed specificity and sensitivity of 100% for diagnosis of myocardial injury in severe cases of scorpion envenomation in relation to Echo measurement. In severe cases, cTnI was positively correlated with IL-8 ($r=0.38$, $P < 0.05$) (Fig. 2) while negatively correlated with %SF ($r=-49$, $P < 0.02$) (Fig. 3) and LVEF ($r=-0.49$, $P < 0.02$) (Fig 4). Furthermore, there were no correlations between the serum values of LDH, CPK or CPK-MB isoenzyme and the measured Echo variables in either severe or moderate cases.

Discussion

Scorpion envenomation is a real health problem in many countries. The mortality of victims of scorpion envenomation admitted to medical ICU is high. Despite the use of sophisticated diagnostic tools and aggressive management, cardiovascular involvement remains the major cause of mortality in scorpion envenomation. The etiology of the cardiac injury in severe scorpion sting is related to the venom effects on the sympathetic nervous system and adrenal secretion of catecholamines as well to the toxic effects of the venom on the myocardium [21]. It is known that scorpion venom contains mixtures of short neurotoxic proteins that act by opening a sodium channel at presynaptic nerve terminals and inhibiting calcium dependent potassium channels. Autonomic storm is thus initiated. Alpha receptor stimulation by the scorpion

Table 2. The serum levels of biochemical markers of myocardiac injury in victim groups and controls on admission.

	No.	LDH (U/L)	CPK (U/L)	CK-MB (U/L)	cTnI (ng/ml)	IL-8 (pg/ml)
I- All patients	41	262.33±23.64	272.7±39.08	213.7±24.89	3.39±0.49	62.63±3.52
II- Severe cases	17	319.7±29.11	380.6±70.14	278.3±42.64	4.73±0.76	72.4±5.25
III- Moderate cases	14	217.7±39.97	158.1±22.91	150.2±23.72	1.03±0.25	52.3±4.94
IV- Mild cases	10	190.6±17.60	129.2±13.89	82.6±8.26	---	40.9±3.12
V-Controls	15	127.3±8.86	65.9± 8.22	14.7±0.89	---	10.6±1.89
P						
Controls versus I		<0.05	<0.01	<0.005	----	<0.005
Controls versus IV		N.S	<0.025	<0.005	----	<0.025
"IV" versus "II"		<0.005	<0.005	<0.005	----	<0.005
"IV" versus "III"		N.S	N.S	<0.05	----	<0.05

Results are expressed as mean ± SE. NS, non significant.

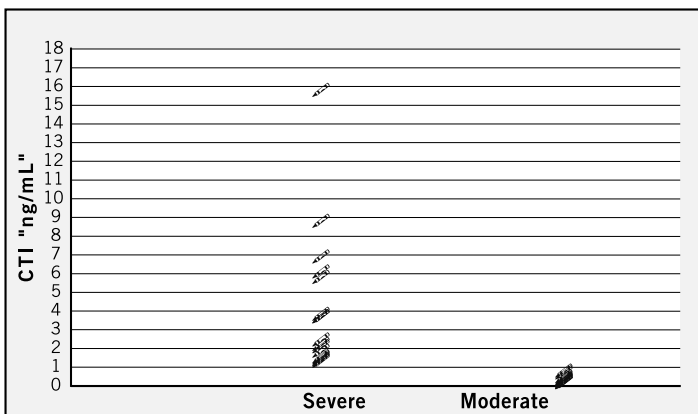


Fig.1: Scattered diagram showing the cut-off value of cTnI level (ng/ml) in patients with severe and moderate envenomation.

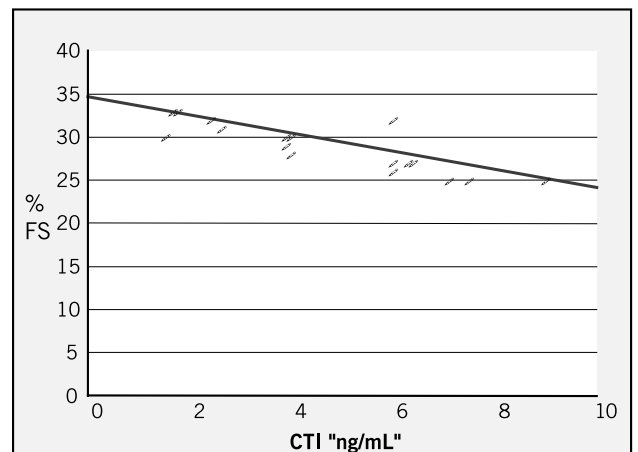


Fig. 3: Correlation between cTnI (ng/ml) and %FS in patients with severe envenomation.

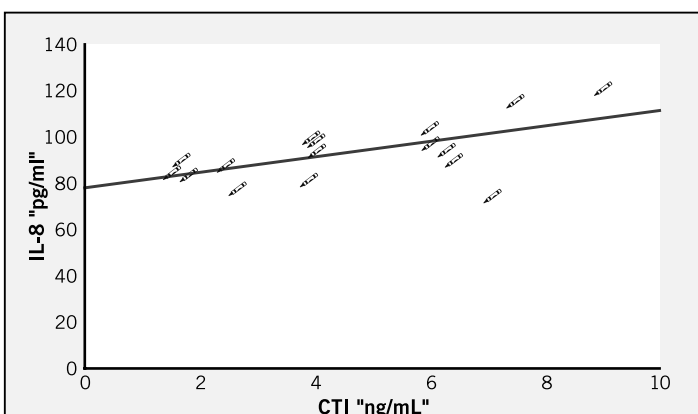


Fig.2: Correlation between cTnI (ng/mL) and IL-8 (pg/mL) in patients with severe envenomation.

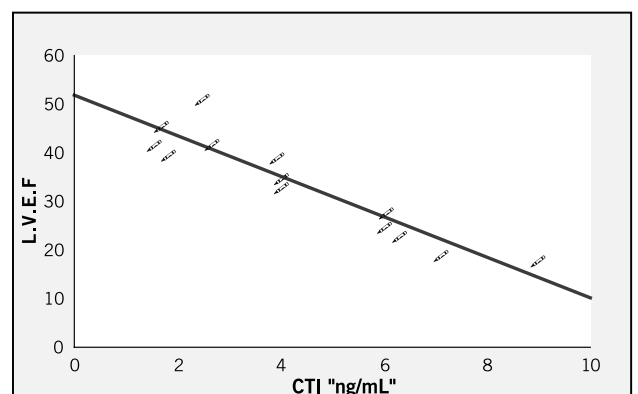


Fig. 4: Correlation between cTnI (ng/ml) and L.V.E.F in patients with severe envenomation.

toxin plays a major role, resulting in hypertension, tachycardia, myocardial dysfunction, increased myocardial oxygen consumption, pulmonary edema and cool extremities [4]. Pulmonary edema in cases of scorpion envenomation has been attributed to left ventricular failure or to increase the pulmonary vascular permeability produced by vasoactive substances released by the toxin. Raised angiotensin I levels have been documented in scorpion envenomation which further facilitate sympathetic outflow through conversion to angiotensin II [7]. Excess catecholamines cause accumulation of endothelins and vasoconstriction. The unopposed effects of alpha receptors stimulation lead to suppression of insulin secretion, hyperglycemia, hyperkalemia, free fatty acids and free radicals accumulation injurious to myocardium. Cardiac sarcolemmal defects, depletion of glycogen content of heart, liver and skeletal muscles were observed in experimental animals with acute myocarditis produced by Indian red scorpion venom [1,22].

In the present study various cardiovascular manifestations were present in children with severe and moderate envenomation (Table 1). This is in keeping with the results of Amitai [23]. The severe cases showed clinical signs suggestive of myocarditis as heart failure, dysrhythmia and ECG changes as well as cardiogenic shock. Also, they showed Echo changes demonstrating the presence of myocarditis and left ventricular dysfunction namely significant reduction of %SF and LVEF in comparison to those of moderate cases (Table 1). The diagnosis Myocarditis in children remains an enigma. On one hand, it is a diagnosis which is more suspected clinically when sudden heart failure or arrhythmia occur, on the other hand the histopathological changes do not coincided with the clinical course. Children may have more deleterious consequences of low-level cardiomyocyte loss than adults due to the length of subsequent survival and an insufficient potential for myocardial growth to compensate for both early damage and somatic development [24].

Several biochemical markers have been used for diagnosis of myocardial injury in scorpion envenomation such as CPK, CK-MB and LDH. In the present study we used these standard markers beside cTnI. The LDH, CPK and CK-MB enzyme activities were significantly higher in all patients in comparison to control group (Table 2), irrespective of the presence of cardiovascular manifestations. Sofer et al. [25] documented the raised CPK in all degrees of scorpion envenomation which reflects the increased skeletal muscle activity due to the sting. A two-to three fold elevation of CPK may follow an intra-muscular injection. CPK-MB isoenzyme exists in the plasma in two forms, named CPK-MB₁, and CPK-MB₂. There is only one CPK-MB isoform in the myocardium, the MB₂. So there is a fundamental problem with CPK-MB protein as it is not a heart specific marker. Larca et al. [26] documented the raised level of CPK-MB isoenzyme in patients with der-

matomyositis. Moreover, the MB₂/MB₁ ratio is not useful when the level of CPK is high due to skeletal muscle injury as in cases of scorpion envenomation. Furthermore, we could not detect any correlation between the serum values of LDH, CPK and CPK-MB isoenzyme and the measured Echo variables in either severe or moderate cases. This was in keeping with the results reported by Amaral et al. [27] who stated that Echo was more sensitive than CK-MB isoenzyme assay in assessing myocardial compromise after scorpion sting. Sofer et al. [25] proved that CPK-MB isoenzyme was significantly higher in patients with cardiovascular signs, but, it lacks a direct relation to the occurrence of myocardial damage.

Recently, Herrmann et al. [28] suggested that cTnI acts as a golden marker of myocardial injury in cases of myocarditis. Moreover, Guest et al., [29] concluded that the magnitude of elevation of serum cTnI correlates with the severity of myocardial damage and predicts cardiovascular morbidity and mortality. In the present study, serum level of cTnI was not detected in the control group as well as in those with mild envenomation. This is in agreement with the results reported by Adams et al. [14] who documented that cTnI does not increase despite severe acute and/or chronic muscle injury even when plasma CK-MB is high unless concomitant cardiac injury is present. The serum levels of cTnI were significantly higher in severe cases in comparison to those with moderate cases in both on admission and on follow up (Table 3). Meanwhile, the SF% and LVEF were significantly reduced among the severe group than those of moderate group. Moreover, cTnI showed significant positive correlation with %SF and LVEF only in severe group (Figs. 3–4). Amaral et al. [27] showed significant decrease of %SF and ECG changes consistent with myocarditis in scorpion envenomation. Das et al., [30] proved that envenomed children with myocarditis had left ventricular dysfunction showed by Echo. The present study revealed that cTnI has specificity and sensitivity of 100% for early diagnosis of myocardial injury in scorpion envenomation. Thus, the estimation of cTnI early in the course of scorpion envenomation may help to detect early the victims at risk for myocardial injury. This is in keeping with Immer et al. [31] who showed that higher specificity of serum cTnI than CK-MB and suggested that the potential use of cTnI for detection of peri-operative myocardial damage in children. The patients of moderate envenomation did not show serum level of cTnI above the "cut-off value" (Fig. I), and the detectable level of cTnI in this group could be explained by the presence of heart failure in these patients as cardiac cell death has been shown to occur in heart failure with release of cTnI. This is in keeping with Lavechia et al., [32] who detected increased serum cTnI in patients with heart failure. In addition, myocarditis may be silent in scorpion envenomation [25]. Moreover, scorpion envenomation may be associated with systemic inflammatory

response syndrome (SIRS) [3]. The SIRS proved to be associated with a significant rise of cTnI [33]. Another support for this finding is the conclusion obtained from the results reported by Lang et al., [34] who concluded that cTnI did not indicate minimal myocardial damage after endomyocardium biopsy. The significant correlation between cTnI and LVFS and %SF were in accordance with the results reported by Briassoulis et al. [13] in cases of adenovirus myocarditis. Similar findings were reported by Herrmann et al. [28].

Cytokines regulate and amplify the immune response, induce tissue injury and mediate complications of the inflammatory response [16]. There is now accumulating evidence to suggest a causal relation between overproduction of pro-inflammatory cytokines and both morbidity and mortality associated with critically ill patients [17]. Wan and Yim, [35] reported that IL-8 as an inflammatory cytokine can be produced locally from the heart which may further enhance leukocyte activation and accumulation in the injured myocardium. Previously, Han et al., [36] detected IL-8 in samples of human heart. Oz et al., [37] hypothesized that human endothelial cells deprived of oxygen would secrete IL-8, which might translate into elevated IL-8 production after cardiac ischemia. The authors suggested that the neutrophil chemoattractant/activator IL-8 may contribute to myocyte injury after prolonged hypothermic cardiac ischemia. In as much as neutrophil activation is a critical initial step in ischemia-reperfusion injury, it has become evident that administration of anti-IL-8 antibodies in rabbit prevents cardiopulmonary injury [38].

Previously, Sofer et al., [39] found that the serum levels of cytokine, IL-6 in cases with scorpion envenomation were significantly higher than controls and still higher after 24 hours post envenomation. In other studies, Barbouche et al., [40] suggested the involvement of pro-inflammatory cytokines in scorpion envenomation and they showed an increase in the levels of IL-1 β and IL-6 in victims compared with controls. Moreover, Meki and Mohey El-Deen [3] showed that IL-1 β and IL-6 are involved in the pathogenesis of scorpion envenomation and correlated with the severity of envenomation. Magalhaes et al. [41] documented the increased levels of IL-6, IL-1 α and interferon gamma in all scorpion-envenomed patients. In the present study, serum IL-8 level was significantly higher in scorpion envenomed children than controls (Table 2). Patients with severe envenomation showed significantly higher mean values of IL-8 than moderate and mild envenomation groups. This finding is in agreement with Endo et al. [42] who considered IL-8 as one of the inflammatory cytokines that reflect the severity of septic shock. The ischemia itself may be an adequate stimulus for IL-8 release. Yasunori et al. [43] proved that IL-8 was released and appeared in the systemic circulation in the very early phase of myocardial injury. In the present study there was significant positive correlation be-

tween IL-8 and cTnI only in patients with severe envenomation with evidence suggestive of myocarditis, although there was no correlation between IL-8 and the SF% or LVEF. This could suggest that IL-8 acts as an indicator for severity of scorpion envenomation. In this respect, Wan and Yim [35] found that the serum levels of cTnI, a highly specific marker of myocardial injury, correlated strongly with IL-8 values in patients undergoing coronary artery bypass grafting indicating that the degree of myocardial injury may be related to IL-8 production.

Case fatality rates of 3–22% were reported among children hospitalized for scorpion stings in India, Saudi Arabia, South Africa and Upper Egypt [45,44,2,3]. The case fatality rate in this study was 12.5%. All the non-survivors were from severe group. In comparison between the survivors and non-survivors of the severe group, only serum level of cTnI was significantly raised on admission in the non-survivors (Table 4). Lavecchia et al. [32] proved that cTnI was significantly correlated with the outcome in patients with myocardial affection in congestive heart failure. Ammann et al. [33] documented the significantly higher serum values of cTnI in non-survivors of septic shock and SIRS, a condition that is reported to occur in scorpion envenomation [3]. Brisassoulis et al. [13] showed that cTnI was significantly higher in the died cases of viral myocarditis. Hirsch et al. [46] stated that in the context of severe acute illness, significant rise of cTnI might be an indicator of poor outcome in children. In this respect, our findings are in accordance with these authors.

In conclusion, the present study is considered the first study which provided evidence that: cTnI is highly specific and sensitive indicator for myocardial injury and adverse outcome in victims of scorpion envenomation. So cTnI may use in these cases for both diagnosis and prognosis. The use of cTnI in the immediate assessment of patients with severe systemic envenomation appears warranted to identify those at risk of myocardial injury. The increased IL-8 levels on follow-up may give reliable information regarding modulation on the immune response following scorpion envenomation and its consequences for the patients outcome. The presence of significant correlation between cTnI and IL-8 only in patients showing evidence of myocarditis raise the question of whether myocardial injury is inflammatory or vascular in nature, as IL-8 reflects both inflammatory and ischemic changes? The elucidation of this point needs further studies. Research along these lines is expected to help in the development of ideal therapeutic strategies to minimize the inflammatory response and subsequent myocardial injury associated with scorpion envenomation.

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