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Study of Cardiac Changes in Egyptian Children with Scorpion Envenomation Before and After Antivenin Therapy

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Scorpionism is an endemic health problem in Upper Egypt. This study shows cardiac complications secondary to scorpion envenomation and establishes the clinical utility of antivenin in reversing this cardiac dysfunction. This study included 40 children (5.9±4.2 years) and 25 healthy age and sex matched controls. They presented to Luxor Hospital after scorpion sting. They were classified into mild, moderate and severe groups. ECG and echocardiographic studies performed for cardiac evaluation. Lactate dehydrogenase (LDH), serum creatinine phosphokinase (CPK), serum CPK- MB and serum cardiac troponin I (cTnI) were studied at admission and 24 h after antivenin therapy. ECG revealed a significant increase in frequency of heart block ($p<0.01$), elevated ST segment ($p<0.05$) and ventricular ectopies ($p<0.01$) in the severe group as compared to the moderate group. Echocardiography revealed significant decrease in left ventricular ejection fraction LVEF% ($p<0.01$) and fractional shortening FS% ($p<0.01$) in severe and moderate cases as compared to mild group. In comparison to mild group the mean values of LDH, CPK, CPK- MB and cTnI were significantly higher in both moderate and severe groups at admission ($p<0.0001$) with significant decrease in both groups after antivenin therapy ($p<0.001$). Non- survivors showed significant reduction in LVEF% and FS% ($p<0.01$) with significant increase in all the biochemical markers in comparison to survivors ($p<0.001$). In conclusion, antivenin therapy is effective in the reversibility of the cardiac changes following scorpion envenomation if given in the first two hours after sting. Delay in treatment may lead to irreversible cardiac damage.

Key words: Cardiac changes, scorpion envenomation, cardiac enzymes, antivenin

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INTRODUCTION

Scorpion envenomation is a life- threatening common event in tropical and subtropical countries. In children it runs more severe course than adults (Meki *et al*., 2003).

Neurotoxins and cardiotoxins are present in the majority of scorpion venoms. The severity of envenomation is related to neurological (Bahloul *et al*., 2005) and cardio-respiratory dysfunction (Diaz *et al*., 2005).

The mechanisms of envenomation induced cardiac dysfunction are still a matter of debate. Some authors suggested a direct effect of the toxin on the myocardium, causing the so called Scorpionic Myocarditis (Mazzei de Davila *et al*., 2002). However, there is general agreement that the cardiovascular effects of scorpion venom are mediated via stimulation of both parts of the autonomic nervous system, with predominance of sympathetic stimulation and the release of tissue and medullary catecholamine (Meki *et al*., 2003). Bahloul *et al*. (2005) explained that myocardial ischemia was not only due to release of catecholamines but also due to the effect of cytokines and/or neuropeptide Y on coronary vessels.

In envenomed children myocardial damage may be clinically occult. Biochemical markers of cardiac injury could be used to ascertain the clinical and echocardiographic findings. Standard biochemical markers namely; creatinine phosphokinase (CPK), creatinine phosphokinase- isoenzyme MB (CPK-MB) and Lactate dehydrogenase (LDH) are useful myocardial injury markers but are non specific. The emergence of monoclonal antibodies to cardiac specific troponin- I (cTnI) showed high efficacy in diagnosing myocardial injury. These antibodies have non cross reactivity with the skeletal muscles (Tamara *et al*., 2003).

Serotherapy of the scorpion envenoming syndrome was a subject of controversy. The effectiveness of the antivenin is influenced by; time of administration, route, dosage, availability, potency and the use of adjuvant or alternative therapy (Hammoudi *et al*., 2004).

The aim of study was first to identify the cardiac changes following scorpion envenomation. Second is to assess the efficacy of antivenin administration in reversing the cardiac dysfunction following scorpion envenomation together with normalization of cardiac enzymes.

MATERIALS AND METHODS

The present study was conducted on 40 children presented to the Emergency Unit and Pediatric Intensive Care Unit (PICU) in Luxor International Hospital with scorpion envenomation from March to June, 2005. They were 25 males and 15 females with a mean age of 5.9±4.2 years, most of the patients presented from rural areas (75%), while (25%) were from urban localization.

Twenty-five apparently healthy children with matchable age and sex attending Pediatric outpatient clinic, National Research Center were served as control group.

According to the severity of envenomation (Ken Dittrich *et al*, 1995), the patients were classified into (Table 1):

Grade I (Mild group): It compromised 9 cases (22.5%) with local pain and/or erythema and/or parasthesia at the site of envenomation.

Grade II (Moderate group): It compromised 14 cases (35%) with pain and/or parasthesia remote from the site of sting. Additional symptoms and signs include tachycardia (≥100 beats/min) or bradycardia (≤60 beats/min), without clinical evidence of carditis, hypo or hypertension (≤3rd or ≥95th percentile for age and sex, respectively), bronchospasm, vomiting and abdominal distension.

Grade III (Severe group): This group included 17 cases (42.5%). They presented with one or more of the following manifestations: (a-) Cardiovascular dysfunction: moderate to severe hypertension., heart failure, cardiac dysrrythmias, myocardial ischemia and pulmonary edema. (b-) Cranial nerve dysfunction: blurred vision, wandering eye movement, hypersalivation, trouble swallowing, problems of upper airways, slurred speech., convulsions and disturbed level of consciousness. (c-) Somatic skeletal neuromuscular dysfunction: abnormal jerky movement of extremities.

Blood collection: At admission, one blood sample was withdrawn for all patients and controls. An additional

Table 1: Descriptive data of envenomed children

	Patients' groups according to severity		
Variable	Mild group (%) (n = 9)	Moderate group (%) (n = 14)	Severe group (%) (n = 17)
Age			
<5 years	33.33 (n = 3)	21.43 (n = 3)	41.18 (n = 7)
5-10 years	44.44 (n = 4)	50.00 (n = 7)	35.29 (n = 6)
>10 years	22.22 (n = 2)	28.57 (n = 4)	23.53 (n = 4)
Time of sting			
Day time	33.33 (n = 3)	28.57 (n = 4)	29.41 (n = 5)
Night time	66.67 (n = 6)	71.43 (n = 10)	70.59 (n = 12)
Site of sting			
Lower limb	66.67 (n = 6)	64.29 (n = 9)	76.47 (n = 13)
Upper limb	22.22 (n = 2)	21.43 (n = 3)	17.65 (n = 3)
Other sites	11.11 (n = 1)	14.29 (n = 2)	5.88 (n = 1)
Type of scorpion			
Yellow scorpion*	88.89 (n = 8)	85.71 (n = 12)	88.24 (n = 15)
Black scorpion**	11.11 (n = 1)	14.29 (n = 2)	11.77 (n = 2)
Time of antivenin initiation in hours		5.8±0.5	6.0±1.2

*Yellow scorpion: *Leiurus* quinquestriatus; **Black scorpion: Buthus occitanus

sample was taken for moderate and severe cases, 24 h after antivenin administration.

Five milliliter of venous blood was withdrawn. Two milliliter of venous blood was added to EDTA for complete blood count. The remainder 3 mL (without anticoagulant) was centrifuged at 2000xg for 15 min; the separated serum was stored at -20°C until assayed.

All patients were subjected to:

- Full history taking with stress on: Age of the patient, time and site of sting, colour of scorpion, local and systemic symptoms and duration between time of sting and start of treatment.
- Thorough clinical examination which included:
  - Vital data of patient:
    Weight, temperature, blood pressure, pulse and heart rate.
  - Local examination:
    Heart, chest, abdomen and neurological examination.
- Imaging procedures:
  - Chest X-ray (postero-anterior and lateral views).
  - Electrocardiography ECG: standard 12 leads.
  - Echocardiography Echo: Two dimensional M mode, Doppler and color flow mapping echo were performed to the studied patients using a sector scanner with 2.5 and 5 MHZ transducers. Examination was performed using Vivid 3 GE Computed Sonografic System.
- Laboratory investigations:
  - Complete blood picture CBC for leukocytosis and hemolysis.
  - Electrolyte evaluation: serum sodium, potassium, calcium and phosphorus (Synchron Cx9 auto analyzer, Beckman instruments, Brea, California).
  - Lactate dehydrogenase(LDH) using UV kinetic kit procedure No 0940, Stanbio Lab, Inc., USA.
  - Serum creatinine phosphokinase (CPK) using UV kinetic kit procedure No 0910, Stanbio Lab, Inc., USA.
  - Serum CPK-MB isoenzyme activity using immunoinhibition method (Cat. No 81779. Diagnostics, Italy).
  - Serum cardiac troponin I (cTnI) using enzyme immunoassay test kit catalogue NoBc-1105. Inc.323 Vintage Park Dr. Foster City, CA 94404.

Treatment protocol

- Supportive measures:
  Chlorpromazine 0.5 mg kg^{-1} intramuscularly for vomiting.
  Diazepam 0.2 mg kg^{-1} intravenously to control convulsions.
  1% local injection of xylocan to control the pain at the site of sting.
- Antivenin was given to moderate and severe cases using purified polyvalent anti -scorpion venom (horse origin) in a dose of 5 mL+ 50 mL saline slowly i.v. over half an hour, to be repeated every two hours up to 20 mL (if the clinical manifestations didn't improve).

Statistical analysis: Data were analyzed with Statistica Software Package V.5 (Statsoft, Tulsa, Ok, USA). Data was expressed as mean ± Standard Deviation (SD). Data were analyzed using Wilcoxon signed rank test Z-test to compare the mean values of different variables. The results were considered to be statistically significant if p values were <0.01. Linear regression analysis was used to assess correlations between the variables.

RESULTS AND DISCUSSION

Scorpion envenomation remains a major health problem in Upper Egypt despite the use of sophisticated diagnostic tools and aggressive management (Meki *et al*., 2003). Cardiovascular involvement is one of the main causes of mortality in those victims (Murthy and Zare, 2002).

The frequency of cardiovascular manifestations were significantly elevated among the severe group as compared to moderate group ($p<0.01$). Tachycardia was the most common presenting manifestation in severe cases, followed by myocarditis, hypotension and hypertension (Table 2). These results were in agreement with Gueron *et al*. (2000), Cheng, (2002), Bawaskar and Bawaskar (2004) and Diaz *et al*. (2005). The mechanisms responsible for the toxic actions of scorpion venom on cardiovascular system are still the subject of intense controversy and research. Most investigators consider that the cardiovascular manifestations are secondary to the peripheral vascular and myocardial effects of scorpion envenomation (Carmen *et al*., 2002). Karnad (1998), detected two hemodynamic patterns following scorpion envenomation. One pattern presented with signs of severe hypertension, tachycardia and increased systemic vascular resistance indices. The other one presented with a predominant myocardial effect with left ventricular dysfunction, tachycardia, pulmonary edema and hypotension. Hypotension is clinically important and a serious medical problem in severe cases of scorpion envenomation. The probable mechanisms of hypotension include a depressive cholinergic effect, a catecholamine

Table 2: Cardiovascular manifestations findings of scorpion envenomed children

Cardiovascular presentation	Severe cases (%) N = 17	Moderate cases (%) N = 14
Tachycardia	70.58	52.0
Myocarditis	52.90	4.3
Hypotension	35.29	43.0
Hypertension	29.41	13.3

depletion syndrome, an exaggerated β_2- vasodilator effect and/or hypovolaemia secondary to excessive fluid loss (Gajanan *et al*., 1999).

The diagnosis of myocarditis in envenomed children remains an enigma. Children may have more deleterious consequences than adults. This may be due to insufficient myocardial growth to compensate for both early damage and somatic development (Lipshultz *et al*., 1997).

ECG study in moderate and severe cases revealed changes in the form of elevated ST segment, heart block and ventricular ectopies. These changes were significantly increased in the severe group of patients when compared to the moderate group ($p<0.01$, $p<0.05$ and $p<0.01$, respectively) (Fig. 1). St segment elevation can result from hyperkalemia and hypocalcaemia. Scorpion venom causes disturbance of trans-membrane K^+ gradient together with blockade of Ca^{++} activated K^+ channels resulting in a state of hypocalcaemia and hyperkalemia. In addition, the venom induced release of catecholamine can cause K^+ efflux from the liver (Amitai, 1998).

Echocardiographic findings pointed out to the existence of cardiac dilatation and left ventricular systolic dysfunction in envenomed children. A significant reduction in the mean percentages of LVEF%, FS% and segmental LV hyperkinesias were noted in severe cases compared to moderate group ($p<0.01$) (Fig. 2). These results were in accordance with Cupo and Hering (2002) and Mazzei de Davila *et al*. (2002). They speculated that the effects are probably due to stunning of the myocardium due to increased myocardial demand. Moreover, Bahloul *et al*. (2004), confirmed the evidence of myocardial hypo perfusion after severe scorpion envenomation.

In the current study, serum biochemical markers for myocardial injury were assayed to augment the clinical and echocardiographic findings of cardiac dysfunction. The LDH, CPK and CPK-MB enzymes activity were significantly increased in all patients in comparison to the control group (Table 3). Furthermore, the severe group of patients showed more significant elevation in the levels of these standard biochemical markers when compared to the moderate group. CPK is not a specific marker as it increases after any intramuscular injection. Similarly CPK-

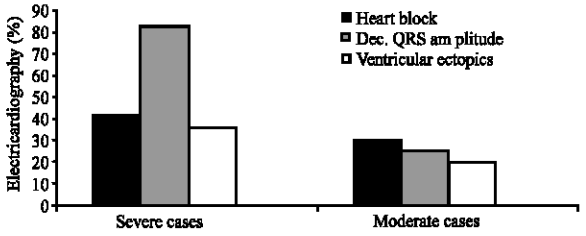

Fig. 1: Electrocardiographic variables among severe and moderate groups

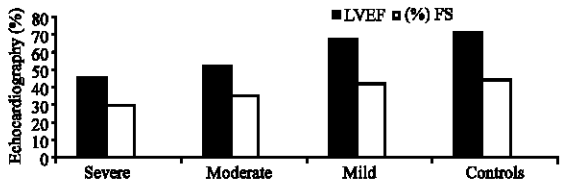

Fig. 2: Echocardiography variables among the studied groups

MB isoenzyme co- exists in the plasma in two forms CPK-MB_1 and CPK-MB_2. The latter is expressed in the myocardium. Therefore, the elevated levels of CPK-MB after scorpion envenomation could not be relayed upon as specific cardiac injury marker (Immer *et al*., 1998). Recently, Herrmann *et al*. (2001) suggested that cTnI serum levels were the golden standard of myocardial injury in cases of myocarditis. In the present study, cTnI levels were not detected in the sera of the control group as well as those with mild envenomation. Moreover, the serum levels of cTnI were significantly higher in severe cases in comparison to moderate cases in both on admission and on follow up (Table 4). These results came in accordance with Guest *et al*. (1995) and Hermann *et al*. (2001). The latter proved that the magnitude of serum cTnI elevation correlated with the severity of myocardial damage.

The present study suggested the great value of early administration of antivenin (within 2 h of exposure) in the reversibility of myocardial damage following scorpion envenomation. The severe group of patients displayed a delay in antivenin administration when compared to the moderate group ($p<0.01$) (Table 5). Cheng *et al*. (2002) proved that antivenin significantly decreased the levels of circulating unbound venom within an hour. The persistence of symptoms after antivenin administration is due to the inability of it to neutralize scorpion toxins already bound to their target receptors.

All the non survivors were from the severe group of patients with toxic myocarditis. These results were concordant with Lavecchia *et al*. (2000) and Mazzei de Davila *et al*. (2002). Bawaskar and Bawaskar (2003)

Table 3: The mean serum levels of biochemical markers of myocardial injury in patients groups and controls on admission

	LDH (mU mL^{-1})	CPK (mU mL^{-1})	CPK-MB (mU mL^{-1})	cTnI (ng mL^{-1})
All patients (n = 40)	605.28 ±92.06	748.53±56.66	50.88±25.7	1.94±0.16
Severe cases (n = 17)	789.18 ±120.6	1216.56±289.9	90.59±25.2	2.49±1.30
Moderate cases (n = 14)	442.64±49.53	152.07±16.56	21.21±5.31	1.70±0.00
Mild cases (n = 9)	308.22±69.44	72.22±13.94	11.33±2.78	ND
Controls (n = 25)	251.33±40.86	65.9±8.22	10.63±4.36	N.D.
Controls versus patients	p<0.05	p<0.01	p<0.01	N.D.
Controls versus mild	p>0.05	p<0.01	p<0.05	N.D.
Mild versus severe	p<0.0001	p<0.0001	p<0.0001	N.D.
Mild versus moderate	p<0.0001	p<0.0001	p<0.0001	N.D.
Moderate versus severe	p<0.0001	p<0.0001	p<0.0001	p<0.0001

Results expressed as mean ±SD. NS = non Significant ND = Not Detect, Significant = p<0.05, p<0.01, Highly significant = p<0.0001

Table 4: The mean serum levels of biochemical markers of myocardial injury in moderate and severe groups on admission and 24 h after antivenin therapy

Biochemical parameters	Envenomed severe cases n = 17			Envenomed moderate cases n = 14		
	At admission	After antivenin	p- value	At admission	After antivenin	p- value
LDH (mU mL^{-1})	798.18±120.6	328.65±85.87	<0.001	442.64±49.53	302.57±83.9	<0.001
CPK (mU mL^{-1})	1216.65±289.9	241.97±45.58	<0.001	152.07±16.56	80.00±13.73	<0.001
CPK-MB (mU mL^{-1})	90.59±25.2	41.41±9.02	<0.001	21.21±5.31	13.57±3.69	<0.001
cTnI (ng mL^{-1})	2.49±1.30	1.36±0.3	<0.001	1.70±0.00	1.34±0.19	<0.001

Table 5: The serum levels of biochemical markers of myocardial injury among the patients with severe envenomation according to the outcome

	Survivors No = 12	Non survivors No = 5	p-value
LDH (mU mL^{-1})	757.42±55.03	896.00±63.93	p<0.05
CPK (mU mL^{-1})	868.17±71.77	1253.00±150.17	p<0.05
CPK-MB (mU mL^{-1})	65.40±13.90	101.08±18.98	p<0.05
cTnI (ng mL^{-1})	2.13±0.23	2.58±2.29	p<0.01
EF%	65.33±40.86	42.9±8.22	p<0.05
FS%	32.14±5.8	19.0±7.6	p<0.01

showed that anti-scorpion venom did not prevent the cardiovascular manifestations of severe scorpion sting. The present study showed that the delay in the administration of antivenin therapy and the development of irreversible cardiogenic shock were the major factors responsible for therapy failure in those victims.

In conclusion, this study demonstrated development of myocarditis and myocardial ischemia in patients with moderate and severe envenomation. It supports the prompt administration of a potent antivenin to these patients. Delay in antivenin therapy (more than 2 h) would contribute to the development of irreversible cardiac damage.

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