

CARDIAC INVOLVEMENT IN DENGUE VIRUS INFECTIONS DURING THE 2004/2005 DENGUE FEVER SEASON IN SRI LANKA

Dominic Wichmann¹, Senanayake Kularatne², Stephan Ehrhardt³, Sriyal Wijesinghe², Norbert W Brattig⁴, Walter Abel⁵ and Gerd D Burchard¹

¹Medical Department - Infectious Diseases and Tropical Medicine, University Hospital Hamburg Eppendorf, Hamburg Germany; ²Department of Medicine, Faculty of Medicine, Peradeniya University, Peradeniya, Sri Lanka; ³Clinical Research, Bernhard-Nocht-Institute for Tropical Medicine, ⁴Department of Molecular Medicine, ⁵Department of Laboratory Medicine, Trauma Hospital Berlin, Germany

Abstract. Sri Lanka experienced a dramatic increase in dengue cases (15,400) in the 2004 - 2005 season. We carried out a prospective study to investigate cardiac involvement in dengue virus infected patients during the 2004 - 2005 season in Peradeniya, Central Province, Sri Lanka. Cardiac involvement was defined as elevated levels of myoglobin, creatine kinase-muscle brain-type, N-terminal pro-brain natriuretic peptide, heart-type fatty acid-binding protein and troponin T. Twenty-five percent of dengue virus infected patients had one or more of the above tests with abnormal results.

INTRODUCTION

According to WHO estimates the growing epidemic of dengue virus infections currently affects approximately 100 countries, causing a substantial health threat in tropical and subtropical regions (Boutayeb, 2006). The disease presents with a broad clinical spectrum from subclinical infection to dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The pathophysiological sequence in severe cases developing circulatory depression is poorly understood. It is believed that cytokine-activation triggered by sensitized

macrophages results in vascular leakage (Rothman, 2003). Some authors reported direct cardiac involvement in dengue fever patients (Obeyesekere and Hermon, 1973; Wali *et al*, 1998; Promphan *et al*, 2004). Our study investigated the extent of myocardial involvement in dengue fever patients, compared with other groups with infectious diseases (Ehrhardt *et al*, 2004, 2005).

From 1998 to 2003 Sri Lankan health authorities annually reported an average of 3,900 dengue fever cases to the South East Asian Regional Office of the WHO (WHO, 2007). Like other countries in the region, Sri Lanka experienced a substantial increase in dengue cases (15,400) in the consecutive 2004/2005 season. From September 2004 to March 2005 we conducted an observational study in 133 adult patients suffering from dengue virus infection at the Peradeniya Teaching Hospital in Peradeniya, Central Province, Sri Lanka, an area endemic for dengue virus.

Correspondence: Dr Dominic Wichmann, University Hospital Hamburg Eppendorf, 1. Medical Department - Infectious Diseases and Tropical Medicine, Martinistr. 52, 20246 Hamburg, Germany.

Tel: ++49 (0)40 7410 51331; Fax: ++49 (0)40 7410 51334

E-mail: wichmann@bni-hamburg.de

MATERIALS AND METHODS

Patients

Patients presenting to the hospital fulfilling clinical criteria for dengue virus infection according to WHO guidelines (WHO, 1997) were enrolled in the study after giving informed consent. The study was approved by the Ethics Committee of the University of Peradeniya, Peradeniya, Sri Lanka.

Serology

Testing for IgM- and IgG-type antibodies against dengue virus was performed by means of a commercial ELISA assay (Panbio Sinnamon Park, Queensland, Australia) according to the manufacturer's protocol. Patients with a positive IgM antibody test and a negative IgG antibody test were classified as having primary dengue infection (PDI) while patients with IgM and IgG antibodies or high titers of IgG antibodies alone were classified as having secondary dengue infection (SDI).

Clinical chemistry

Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a sensitive marker for impaired left ventricular function, and heart-type fatty acid-binding protein (h-FABP), sensitive and specific for acute myocardial injury, were measured (Ehrhardt *et al*, 2005). Cystatin C (CyC), a marker of glomerular filtration (Furuhashi *et al*, 2003), myoglobin, creatine kinase-muscle brain (CK-MB), and troponin T (TnT), established markers of myocardial injury, were measured as described elsewhere (Ehrhardt *et al*, 2005). Frequencies were compared by chi-squared tests.

RESULTS

From September 2004 to April 2005, 133 patients aged 18 to 76 years old (median 30) were included in the study. Of these, 64

(52%) were female. After serological testing for IgM- and IgG-type antibodies, 67 patients were classified as having PDI and 66 as having SDI. Cardiac involvement, as defined by elevated cardiac enzymes, was found in both subgroups (Table 1). A correlation with age, gender, or diseases predisposing to myocardial impairment, such as hypertension or renal insufficiency, could not be demonstrated. Myoglobin was elevated in 43.3% of PDI patients and in 50.1% of SDI patients. Abnormal results for CK-MB, TnT, h-FABP and NT-proBNP were found in 14.9% and 16.2%, 1.5% and 1.5%, 5.9% and 4.8% and in 22.4% and 16.1%, in PDI and SDI patients, respectively. Elevated levels of CyC were seen in 17.9% of PDI and 30.3% of SDI patients.

DISCUSSION

We have demonstrated myocardial involvement in dengue virus infection defined by elevated cardiac markers for the first time in a moderate sized prospective study. These results are consistent with previous findings from our and other groups with various infectious conditions, such as malaria and bacterial sepsis (ver Elst *et al*, 2000; Ehrhardt *et al*, 2005).

These findings should be interpreted with caution since most of these parameters are influenced by renal function (Furuhashi *et al*, 2003). When we stratified our data into those with normal and impaired renal function, only NT-proBNP serum levels were more often elevated in patients with elevated CyC ($p < 0.0001$). All other cardiac markers were evenly distributed across the strata. Overall, cardiac markers were only moderately elevated, as seen with CyC (Table 1). The high frequency of renal impairment, was surprising (elevated levels of CyC in 20.3%). Our results are tempered by the fact that apart from one fatal case, none of our patients fulfilled WHO criteria for dengue

Table 1
 Ranges of cardiac markers in patients with primary dengue virus infection (PDI) and secondary dengue virus infection (SDI).
 Median-values are shown in parentheses. Overall fractions of elevated markers are given irrespective of age, gender or the type
 of infection (PDI or SDI).

Biochemical markers	Cut-off levels	PDI (n = 67)	SDI (n = 66)	Overall percentage of elevated markers (No./%)
Myoglobin (female)	< 58 mg/l	33 - 260 (71)	29 - 251 (75)	60/45.1%
(male)	< 72 mg/l	49.3 - 855 (68)	28.8 - 612 (75.1)	
CK-MB (female)	< 3.77 mg/l	0.6 - 4.7 (1.7)	0.6 - 7.2 (3.3)	17/12.8%
(male)	< 6.73 mg/l	0.6 - 11.1 (2.6)	0.5 - 509 (2.3)	
Troponin T	< 0.01 mg/l	0.01 - 0.09 (0.01)	0.01 - 0.02 (0.01)	1/0.8%
h-FABP	< 1.6 mg/l	0.0 - 11.5 (0.5)	0.0 - 11.2 (0.74)	7/5.3%
NT-proBNP (female)	< 50 years: < 155 ng/l > 50 years: < 222 ng/l	8.0 - 432 (62)	7.9 - 274 (52)	25/18.9%
(male)	< 50 years: < 84 ng/l > 50 years: < 194 ng/l	16.4 - 1,935 (48)	37.2 - 700 (84)	
Cystatin C	< 0.96 mg/l	5.2 - 193 (55.9)	11.3 - 1,925 (48)	
		0.42 - 1.26 (0.74)	13.5 - 1,392 (86)	32/25.1%
			0.42 - 1.32 (0.88)	

CK-MB, creatine kinase-muscle brain; NT-proBNP, n-terminal pro-brain natriuretic peptide; h-FABP, heart-type fatty acid-binding protein. As indicated, for some parameters different cut-off levels exist for male and female patients as well as for different age groups.

hemorrhagic fever or dengue shock syndrome, and could not be categorized as severely ill. Previous reports of cardiac involvement have concentrated on children and juveniles (Kabra *et al*, 1998), which is different from our study population. Children and juveniles bear the largest burden of dengue virus infections and thus further studies should focus on these groups. Myocardial involvement in patients with infectious diseases is an often unrecognized and underestimated problem and warrants further investigation (Spies *et al*, 1998; ver Elst *et al*, 2000).

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