JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 1, 2023; 26-33
https://doi.org/10.19106/JMedSci005501202304

Comparison of cardiac marker profiles in dengue myocarditis

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Submitted: 2022-06-04
Accepted : 2022-10-15

ABSTRACT

Dengue patients may experience some grade of severity. Cardiac involvement is common in severe dengue, therefore cardiac markers could be used to ensure the diagnosis of dengue myocarditis. However, information of the cardiac marker profiles in patients with milder severity of dengue infection is limited. The study aimed to evaluate creatinine kinase (CK), creatinine kinase-MB (CK-MB) and troponin I (TnI) in dengue myocarditis against the spectrum severity of dengue infection in children. This cross-sectional study was conducted using secondary data from medical records of dengue myocarditis patients aged 1-18 yr in Dr. Sardjito General Hospital, Yogyakarta. Fisher's Exact tests were performed to compare the increase in cardiac markers to the dengue severity. The increase of CK was observed in dengue fever/DF (6 or 75% of patients), dengue hemorrhagic fever/DHF (6 or 67%) and dengue shock syndrome/DSS (16 or 73%). Furthermore, the increase of CK-MB was also observed in DF (6 or 75%), DHF (8 or 87%), and DSS (21 or 95%). No significant difference in the increase of CK and CK-MB proportions was observed in DF compared to DHF groups and in DF compared to DSS ($p>0.05$). The increase of Tn I was observed in DHF (2 or 22%) and DSS (10 or 45%) groups but not observed in DF group. Significant difference in the increase of Tn I proportion was observed in DF compared to DSS groups ($p=0.022$). In conclusion, cardiac involvement is common in all dengue severity level. The increment of Tn I corresponds to an increase in the dengue severity level. Further research by observing cardiac markers sequentially is needed.

ABSTRAK

Pasien dengue kemungkinan mengalami berbagai spektrum derajat keparahan. Keterlibatan jantung umumnya terjadi pada dengue berat sehingga petanda jantung dapat digunakan untuk menegakkan diagnosis. Namun demikian, informasi profil petanda jantung pada dengue dengan keparahan lebih ringan sangat terbatas. Penelitian ini bertujuan mengkaji kreatinin kinase (CK), kreatinin kinamse-MB (CK-MB) dan troponin I (TnI) pada mikokarditis dengue pada anak dengan dengan derajad keparahan infeksi dengue. Penelitian dengan rancangan potong lintang ini menggunakan data rekam medis pasien usia 1-18 tahun dengan miokarditis di RSUP Dr. Sardjito, Yogyakarta. Uji Fisher Exact digunakan untuk menganalisis perbedaan kenaikan penanda jantung dengan tingkat keparahan infeksi dengue. Kenaikan kadar CK teramati pada *dengue fever*/DF (6 atau 75% pasien), *dengue hemorrhagic fever*/DHF (6 atau 67%), *dengue shock syndrome*/DSS (16 atau 73%). Selanjutnya, kenaikan CK-MB juga teramati pada DF (6 atau 75%), DHF (8 atau 87%) dan DSS (21 atau 95%). Tidak terdapat perbedaan dalam proporsi kenaikan CK dan CK-MB antara kelompok DF dibandingkan dengan DHF dan DF dengan DSS ($p>0.05$). Kenaikan Tn I teramati pada DHF (2 atau 22%) dan DSS (10 atau 45 %), tetapi tidak teramati pada kelompok DF. Perbedaan nyata dalam kenaikan proporsi Tn I teramati pada kelompok DF dibandingkan dengan DSS ($p<0.022$). Dapat disimpulkan, keterlibatan jantung umumnya terjadi pada semua tingkat keparahan dengue. Peningakatan Tn I berhubungan dengan peningkatan tingkat keparahan dengue. Penelitian lanjutan untuk memantau petanda jantung secara berkala diperlukan.

Keywords:
cardiac marker;
dengue;
myocarditis;
creatinine kinase;
troponin I

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INTRODUCTION

Dengue is a viral infection caused by the dengue virus (DENV) which is transmitted to humans by infected mosquito bites. Around 390 million cases of dengue infection are reported annually, with 96 million of them have clinical manifestations. America, South-East Asia, and Western Pacific regions are the most severely affected regions, with Asia accounting for 70% of the global disease burden.[1] In Indonesia in 2020, 108,303 patients with dengue hemorrhagic fever (DHF) were reported with 747 of them died.[2] Children are particularly vulnerable to dengue infection in Indonesia with the incidence of cases aged 0-14 years was 53.08% in 2019.[3]

Dengue patients may experience a spectrum of clinical conditions, ranging from asymptomatic, mild dengue fever (DF) to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which can be fathal.[4] Myocarditis is the most common manifestation of dengue.[5] A study in Brazil reported that 12 (15%) of 81 dengue patients have elevated cardiac biomarkers (troponin I/Tn I and pro-B-type natriuretic peptide).[6] Another study in Sri Lanka reported that 75 (62.5%) of 120 dengue patients diagnosed by serological testing show varying electrocardiography (ECG) abnormalities including T inversion, ST depression, and bundle branch block.[7] In Indonesia, the study of dengue myocarditis especially on pediatric patients is limited. A prospective cohort study in Indonesia reported that myocarditis dengue is diagnosed in 39 out of 50 pediatric dengue patients.[8]

Myocarditis is defined as inflammation of the myocardium. The pathophysiology of cardiac involvement in dengue cases is not clearly understand. Myocardial involvement in dengue can occur due to direct viral invasion of the heart muscle, damage caused by cytokines due to immune reactions, or both. Elevated levels of tumor necrosis factor alpha (TNF-α), interleukin (IL) 6, 13, and 18, and cytotoxic factors in patients with dengue may lead to increased vascular permeability and shock. Dengue virus antigen has been shown to play a role in inflammatory cells in the heart, and dengue virus has been shown to cause damage to the heart experimentally. The virus or viral RNA was detected in various tissues, including the kidneys, heart, lungs, and brain in cases of dengue death. A new hypothesis suggests that impaired calcium (Ca^{2+}) storage in infected cells contribute directly to myocarditis.[8]

The wide range of clinical manifestations and the difficulty of diagnosing myocarditis make the incidence difficult to be quantified. Signs of myocarditis can range from a subclinical rise in biomarkers or the presence of ECG abnormalities in asymptomatic cases, to more overt manifestations such as shortness of breath, chest pain, and sudden death. Testing of the levels of serum cardiac markers [creatine kinase (CK), Tn I and T] are routinely performed in suspected cases of myocarditis.[9] Endomyocardial biopsy and cardiac magnetic resonance imaging (MRI) can improve the accuracy of the diagnosis of myocarditis. However, these procedures are either considered too invasive or not widely available in dengue endemic areas.[10]

The aim of this study was to compare levels of the cardiac markers i.e. CK, CK-MB and Tn I in dengue myocarditis

with the severity of dengue infection in children. Appropriate information of cardiac inflammation marker relating dengue infection severity would increase the awareness of possibility myocarditis earlier.

MATERIALS AND METHODS

Design and subject

This cross-sectional study was conducted using secondary data of patients' medical records with diagnosis of dengue myocarditis at Dr. Sardjito General Hospital, Yogyakarta, Indonesia in the period July 2015 - May 2016. All patients aged 1-18 yr diagnosed with dengue myocarditis were included in this study.

Protocol of study

Dengue infection was diagnosed according to the World Health Organization (WHO) 2011 guidelines with a positive antidengue IgM/IgG serology test or positive nonstructural protein 1 (NS-1) test. Myocarditis was defined as patients with an increase of one or more serum cardiac markers (CK, CK-MB, or Tn I) and/or had ECG abnormalities. Laboratory examination of cardiac markers and ECG recording were conducted in the period of day 4-6 of fever, in order to get the most possible differences in cardiac function between patients with or without plasma leakage.[11] Patients with a history of previous heart disease, either congenital or acquired, were excluded from the study. Assuming a prevalence of 15% for pediatric dengue with abnormality of cardiac marker,[5] the Type-I error of 5%, and also based on the 95% confidence interval, the minimum required sample size of 50 patient was calculated.

Patient characteristics were collected from medical records including age, severity, outcome, days of fever, presence of bleeding manifestations, plasma leakage, hepatomegaly, routine peripheral blood test result, ECG characteristics, and levels of CK, CK-MB, and Tn I.

Statistical analysis

Fisher's Exact tests were performed to compare the increase in cardiac markers in dengue myocarditis to the severity. A p value < 0.05 was considered significant.

RESULTS

A total of 39 patients with dengue myocarditis were involved in this study. Characteristics of patients are presented in TABLE 1. Among 39 patients with dengue myocarditis, 8 (21%) were categorized as DF, 9 (23%) as DHF, and 22 (56%) as DSS. Dengue myocarditis patients mostly came to the hospital on days 3-5 of fever. Plasma leakage occurred in 9 (23%) cases, and pleural effusion was the most common form of plasma leakage. All of the patients survived during the study period.

TABLE 1. Clinical and laboratory (routine peripheral blood test) profile of dengue myocarditis patients (n=39)

Variables	Total
Clinical profile	
Age [n=39; n (%)]	
• < 5 y	15 (38)
• ≥5 y	24 (62)
Degree of severity [n=39; n (%)]	
• DF	8 (21)
• DHF	9 (23)
• DSS	22 (56)
Outcome [n=39; n (%)]	
• Died	0 (0)
• Survived	39 (100)
Day of fever [n=39; n (%)]	
• <72 hr	8 (21)
• 3-5 d	22 (56)
• ≥ 6 d	9 (23)
Hemorrhagic sign [n=14; n (%)]	
• Petechiae	5 (13)
• GIT bleeding	7 (18)
• Epistaxis	2 (5)
• Gum bleeding	2 (5)
Plasma leakage [n=9; n (%)]	
• Pleural effusion	6 (15)
• Ascites	4 (15)
Hepatomegaly [n=39; n (%)]	
• Hepatomegaly	26 (67)
• No hepatomegaly	13 (33)
Laboratory profile	
Hemoglobin (mean ± SD g/dL)	13.43 ± 2.02
Hematocrit (mean ± SD %)	38.52 ± 5.69
Platelet [med (min-max) cell/μL]	31 (4-501)
Leucocytes [med (min-max) cell/L]	4.9 (1.28-34)
NS-1 positive [n (%)]	16 (41)
IgM anti dengue positive [n (%)]	25 (64)
IgM & IgG anti dengue positive [n (%)]	18 (46)

TABLE 2. Characteristics of ECG abnormalities of dengue patients according to the disease severity (n=22)

Description	Degree of severity			Total
	DF [n (%)]	DHF [n (%)]	DSS [n (%)]	n (%)
Sinus tachycardia	2 (18)	4 (36)	5 (46)	11 (50)
Sinus bradycardia	1 (25)	0 (0)	3 (75)	4 (18)
Low voltage	0 (0)	1 (20)	4 (80)	5 (23)
Sinus tachycardia and low voltage	0 (0)	0 (0)	2 (100)	2 (9)
Total	3 (14)	5 (23)	14 (63)	22 (100)

DF=dengue fever; DHF=dengue hemorrhagic fever; DSS= dengue shock syndrome.

TABLE 3. Characteristics of cardiac marker abnormalities of dengue patients according to ECG abnormalities

Cardiac marker	ECG abnormalities			
	Sinus tachycardia	Sinus bradycardia	Low voltage	Sinus tachycardia & low Voltage
CK [n (%)]				
• Normal	1 (9)	0 (0)	1 (20)	0 (0)
• Increase	10 (91)	4 (100)	4 (80)	2 (100)
CK-MB [n (%)]				
• Normal	2 (18)	0 (0)	0 (0)	0 (0)
• Increase	9 (82)	4 (100)	5 (100)	2 (100)
Tn I [n (%)]				
• Normal	5 (45)	2 (50)	1 (20)	0 (0)
• Increase	6 (55)	2 (50)	4 (80)	2 (100)

ECG=electrocardiogram; CK=creatine kinase; CK-MB=creatine kinase – myocardial band.

Comparison of cardiac marker abnormalities to the dengue severity is presented in TABLE 4. The increase of CK was reported in DF (6 or 75% of patients), DHF (6 or 67%) and DSS (16 or 73%). Moreover, the increase of CK-MB was also observed in DF (6 or 75%), DHF (8 or 87%), and DSS (21 or 95%). There was no significant difference in the increase of CK and CK-MB proportions in DF compared to DHF groups and in DF compared to DSS ($p>0.05$). The increase of Tn I was observed in DHF (2 or 22%) and DSS (10 or 45%) groups but not observed in DF group (0 or 0%). Significant difference in the increase of Tn I proportion was observed in DF compared to DSS groups ($p=0.022$).

TABLE 4. Comparison of cardiac marker abnormalities to the severity of dengue (n=39)

Cardiac marker	Degree of severity			p*
	DF	DHF	DSS	
CK [n (%)]				
• Normal	2 (25)	3 (33)	6 (27)	0.563[a]
• Increase	6 (75)	6 (67)	16 (73)	0.645[b]
CK-MB [n (%)]				
• Normal	2 (25)	1 (13)	1 (5)	0.453[a]
• Increase	6 (75)	8 (87)	21 (95)	0.166[b]
Tn I [n (%)]				
• Normal	8 (100)	7 (78)	12 (55)	0.265[a]
• Increase	0 (0)	2 (22)	10 (45)	0.022[b]

*Fisher's exact test; DF=dengue fever; DHF=dengue hemorrhagic fever; DSS= dengue shock syndrome; [a]DF vs DHF; [b]DF vs DSS.

DISCUSSION

Characteristics of patients with dengue myocarditis in children in the Dr. Sardjito General Hospital, Yogyakarta was reported (TABLE 1). The profile of ECG abnormalities according to severity showed that the most ECG abnormalities occurred in the DSS group. Decreases in intravascular volume and in preload will affect the coronary microcirculation, causing damage to the myocardium which can interfere with contractility and heart rhythm.[10] The results of this study are in line with research conducted by Hussain *et al,*.[12] regarding the ECG profile in dengue infection in children in Indonesia.

This current study showed that there was no effect of the proportion of increased levels of CK and CK-MB on the severity of dengue (DF vs. DHF and DF vs. DSS). The insignificant result could be due to the low positive predictive value (PPV) of CK and CK-MB in assessing myocardium injury. The PPV of CK value is 40.5%, while the CK-MB is 64.9%. Therefore, it was prone to have false positive results. The results in this study are similar to the findings of Li *et al.*,[13] where the increase in CK-MB levels was higher in the non-severe dengue group with warning signs (34.29%) than non-severe dengue without warning signs (25.30%). However, it was not statistically significant (p=0.276).

The proportion of increased troponin I levels was not significant between the DHF group compared to the DF group (p=0.265). However, the proportion of increased Tn I levels was significant between the DSS group compared to the DF group (p=0.022). This finding showed that increased proportions of Tn I levels may be associated with the severity of dengue (DF vs. DSS). This may happen because in shock conditions there is a release of TNF-α in large quantities which causes a decrease in blood pressure or shock and hypoperfusion, whereas in the DF and DHF groups there is no hypoperfusion. Hypoperfusion conditions that occur in DSS will cause a decrease in the integrity of myocyte membranes and changes in coronary microcirculation, causing damage to the myocardium and the release of Tn I.[8,14,15]

Kularatne *et al.*,[7] reported that 29% of dengue patients with cardiac involvement had increased Tn T levels, where 12% of these occur in patients who had shock.[7] In addition, Iskandar *et*

al.,[15] reported that Tn T levels are higher in the DSS group compared to DHF. However, this study differs from the study conducted by Yacoub *et al.*,[16] of 17 patients who had Tn I levels checked, one patient with severe dengue had elevated Tn I levels, and 16 other patients with varying degrees of severity had normal Tn levels. The difference may occur due to the difference in the cut-off point of Tn I levels used. The study used a cut-off point of 0.3 ng/mL, while in our current study a cut-off point of 0.01 ng/mL was used with a sensitivity of 88.1% - 100% and a specificity of 79.9% - 96.3%.[7] Another marker such as amino-terminal pro-brain natriuretic peptide (NT-proBNP) can be used to detect myocardial injury, and this inflammatory activity can be confirmed by a higher leukocyte count and C-reactive protein levels.[6]

Even though cardiac troponins are the standard test used to diagnose acute myocardial infarction, however, those may be elevated in cases related to non-cardiac causes. Elevated levels of cardiac troponins can occur due to end-stage renal disease, strenuous exercise, sepsis, and rhabdomyolysis, acute pulmonary edema, chronic obstructive pulmonary disease, pulmonary hypertension, stroke, and subarachnoid hemorrhage.[17,18] These conditions may increase cardiac troponin concentration in the blood due to a mismatch between cardiac oxygen supply and demand even in the absence of coronary artery disease.[18]

Myocarditis can worsen the clinical outcome of patients with dengue infection with shock. Myocarditis causes a decrease in the left ventricular ejection fraction which will decrease the cardiac output and aggravate shock condition. This needs to be monitored closely since the initial management of dengue myocarditis in order not to further worsen the clinical course of the disease. Severe and prolonged shock conditions will also reduce the integrity of the myocyte membrane and affect the coronary microcirculation, causing the exacerbation of the myocarditis itself.[8-10]

Our study had a limitation in that the cardiac marker examination was only performed once during the hospitalization period, therefore it was not possible to detect changes in the cardiac marker levels during the dengue infection phase. The number of subjects did not meet the minimum calculated sample size; thus, the power of the study was not high. This condition was unavoidable since there was a limitation on the length of the study. Further research using a higher number of subjects and serial monitoring of cardiac enzymes are needed to confirm the role and kinetics of cardiac markers in dengue myocarditis.

CONCLUSION

In conclusion, Tn I level shows a significantly rise in the DSS spectrum of dengue infection parallel with increasing severity. A follow-up monitoring of the level of cardiac markers as well as ECG abnormality should be performed to understand more about dengue myocarditis characteristics in pediatric patients.

ACKNOWLEDGEMENT

Authors would like to thank the Director of Dr. Sardjito General Hospital, Yogyakarta for his support during the study.

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