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The role of myocarditis in the acute phase of Kawasaki as a predictor of the future coronary aneurysm: a case–control study

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Abstract

Background: This study aimed to evaluate the relationship between cardiac troponin I and T (cTnI, cTnT) and creatine kinase (CK)-MB during the acute phase of Kawasaki disease (KD) and the development of coronary artery involvement (CAI).

Results: Ninety children diagnosed with KD and 38 attending ambulatory clinics as controls were enrolled in this study. Serum levels of cardiac enzymes were measured in all case and control groups. Serial echocardiograms were performed in KD patients during the acute, subacute and convalescence phases. Thirty-six percent of patients had CAI during the acute phase of KD; this rate was 21% and 18% in the echocardiography in the sub-acute and convalescent-phase, respectively. Elevated serum cTnI and cTnT levels were seen in 15.5% and 10% of KD patients, respectively, but not in the controls ($P < 0.01$). Patients with abnormal echocardiography had significantly higher levels of CK-MB but cTnI and cTnT. Cardiac troponins have high specificity, and CK-MB had a high sensitivity for predicting CAI in KD.

Conclusion: Subclinical myocarditis occurs during KD, and serum cardiac troponin levels are significantly elevated, but cardiac biomarkers cannot predict CAI in the future.

Background

KD is a systemic medium vessel vasculitis of childhood, mainly affecting infants and children under five (Agarwal and Agrawal 2017). The etiology of KD is unknown; however, it has been suggested that it is caused by an infectious trigger in individuals with and genetic predisposition (Rowley 2018). Although KD is a multi-system disease, it has a predilection for the cardiovascular system, particularly coronary arteries. It is known as the leading cause of pediatric acquired heart disease in developed countries (Agarwal and Agrawal 2017; Rowley 2018; Duarte et al. 2010).

CAI is the primary clinical concern in KD since they are the main determinant of its outcome (Duarte et al. 2010; Senzaki 2008). They characteristically occur during the subacute phase of KD, with an incidence ranging from < 5% in effectively treated to approximately 25% in untreated patients. They are associated with thrombosis or stenosis of coronary arteries and, subsequently, myocardial infarction, sudden death, or congestive heart failure (Duarte et al. 2010). Moreover, non-coronary cardiovascular complications such as myocarditis, myocardial dysfunction, pericarditis, pericardial effusion, valvular dysfunction and congestive heart failure may also develop during the acute phase of the disease (Duarte et al. 2010; Hematian et al. 2015; Kumar Mandal and Sahoo 2012).

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KD-associated myocarditis is much more common than CAI, its histopathological features being found in 100% of post-mortem and live cardiac biopsies in KD patients (Harada et al. 2012; Yutani et al. 1981). Hiraishi et al. found no correlation between the occurrence of CAI and the electrocardiographic, echocardiographic, radiographic and clinical signs of myocarditis (Hiraishi et al. 1981). On the other hand, according to Lega et al., echocardiographic signs of myocarditis can predict coronary artery lesions during the acute phase of KD but not in the convalescent phase (Lega et al. 2013). However, most cases of myocarditis are subclinical and, as a result, are not diagnosed by clinical manifestations or routine electrocardiographic or echocardiographic tests (Dionne and Dahdah 2018).

Given the high rate of subclinical myocarditis in the acute phase of KD, serum biomarkers have been recommended as a diagnostic tool for KD-associated myocarditis (Sato et al. 2013). cTnI and cTnT are heart-specific biomarkers expressed after myocardial cell injury and have been suggested for prognostic assessment and clinical management of myocarditis (Janardhanan 2016; Eggers and Lindahl 2017). CK-MB is also increased during acute myocyte injury; however, it is less sensitive and specific than cTnI for detecting myocarditis and is not heart-specific (Bodor 2016). Kim and Kim (1999) reported significantly increased levels of cTnI and CK-MB in the acute febrile stage of KD. However, they found no correlation between the level of cardiac markers and coronary artery lesions due to the small number of patients with such lesions in the acute phase of KD. On the other hand, another study has reported no significant increase in cTnI levels in KD patients and no correlation between cTnI levels and myocarditis or subsequent development of coronary artery lesions (Checchia et al. 2001).

Given the importance of CAI in the prognosis of KD and the lack of consensus on the role of biomarkers in predicting coronary artery abnormalities, this study aimed to evaluate the relationship between cardiac biomarkers (cTnI, cTnT and CK-MB) serum levels and coronary artery abnormalities during the acute phase and also subsequent development of CAI during the subacute phase of KD.

Methods

The present prospective case–control study aimed to assess the value of cTnI, cTnT and CK-MB serum levels as a marker of KD-associated myocarditis in predicting subsequent CAI. The Ethics Committee approved the study of Tehran University of Medical Sciences. Written informed consent was obtained from the parents/guardians of each enrolled patient. According to the attending rheumatologist's orders and local practice guidelines, all participants received the standard care for KD.

Study subjects

The study was performed on 90 children diagnosed with KD admitted to Children's Medical Center, Tehran, Iran, during the febrile stage of the disease between 2015 and 2018, and 38 children attending ambulatory clinics at Children's Medical Center during the same period as controls. All patients were diagnosed with either complete or incomplete KD according to the criteria of the American Heart Association (Newburger et al. 2004). Children with concomitant inflammatory pathologies, chronic cardiac or renal disease, immune-deficiency problems, or bacterial or viral infection were excluded. The study also comprised two control groups, 18 febrile children who attended in general pediatric clinic with flu-like symptoms and 20 afebrile children who attended our well-baby clinic for routine anthropometric measurements or vaccination. All parents signed the informed consent, and the Ethics Committee approved the study at the Tehran University of Medical Sciences.

Serum levels of cTnT, cTnI and CK-MB were measured in KD patients and both control groups. Moreover, serial transthoracic echocardiograms were obtained from KD patients during the acute phase and 10–14 days and 6–8 weeks later.

Biomarker's assessment

cTnI and cTnT were measured in all patients by an electro-chemiluminescent immunoassay (ELECSYS 2010, ROCHE, France). According to the reference ranges recommended by the manufacturer, serum cTnI level > 0.3 ng/ml and cTnT level > 25 pg/ml were considered suggestive of cardiac damage. Similarly, the levels of CPK and CK-MB were measured by an electro-chemiluminescent immunoassay (COBAS INTEGRA 400 plus, ROCHE, France). CK-MB was considered positive if its serum level was > 25 IU/L or > 25% of the total CPK. The plasma sample was perfumed from all KD patients before treatment with IVIG.

Echocardiography

All KD patients underwent transthoracic two-dimensional echocardiograms at least three times during the acute phase, at the beginning of the subacute phase (10–14 days after the first echocardiogram) and during the convalescence phase of the disease (6–8 weeks after the first echocardiogram). All patients were evaluated by the same cardiologist and conducted echocardiogram (Samsung HS70 device 8–12 and 4–8 probes sizes). Echocardiographic views of coronary arteries included the right and left main coronary artery (RCA and LMCA), left

circumflex (LCX) proximal segment and left anterior descending (LAD).

Statistical analysis

Statistical analysis was performed using the SPSS software package, Version 21. The Wilcoxon rank-sum test for nonparametric variables analyzed mean ages and day of illness data. cTnI, cTnT and CK-MB values were compared among the three groups (KD patients, febrile controls and afebrile controls) using the Kruskal–Wallis one-way analysis of variance. Significance was determined as a p-value < 0.05.

Results

Participants' clinical and laboratory characteristics

This study evaluated 128 children (59.3% boys, 40.7% girls, mean age of 3.9 years). Of these, 90 children were diagnosed with KD (51 incomplete and 39 complete KD). The remaining 38 participants were enrolled as controls (20 as healthy controls and 18 as febrile controls). Compared to complete KD, patients with incomplete KD had a significantly longer duration of fever before diagnosing KD, higher PLT count and lower hemoglobin. On the other hand, serum CRP, ALT and ALK levels were significantly higher incomplete KD patients. Clinical and laboratory characteristics of KD and control groups are shown in Table 1.

Echocardiographic findings

Of the 90 KD patients, 36% had coronary artery dilatation (including aneurism or ectasia), and 4% showed transitory changes such as brightness and lack of tapering in their first echocardiography during the acute phase of the disease. The rest had normal echocardiograms. The second echocardiography performed during the subacute phase revealed normal findings in 79% of patients. However, 21% of patients still had CAI. CAIs were still detectable in the last follow-up echocardiograms in 18% of patients. To assess the course of CAI regression, KD patients were categorized into three groups: patients with three normal echocardiograms (60%), patients in whom CAI regressed during the follow-up period (22%), and patients with persistent CAI (18%). The frequency of CAI in each echocardiography and transient and persistent echocardiographic changes was significantly higher in incomplete KD patients than in complete KD ($P < 0.01$).

Cardiac biomarkers

cTnI and cTnT levels were significantly increased in KD patients compared to controls ($P < 0.02$, Table 2). Elevated serum cTnI (> 0.3 ng/ml) and cTnT levels (> 25 pg/ml) were recorded in 12.8% and 10.2% of patients with complete KD and 17.6% and 9.8% of patients with incomplete KD but in none of the controls. There was no statistically significant difference between complete and incomplete

Table 1 Clinical and laboratory characteristics of participants with Kawasaki disease, febrile and healthy controls

Participants' characteristics	Complete KD ($n = 39$)	Incomplete KD ($n = 51$)	Febrile controls ($n = 18$)	Healthy controls ($n = 20$)	P-value
Median age (range)/ years	3.9 (± 2.1)	2.6 (± 2.8)	5.3 (± 3.4)	6.2 (± 3.5)	0.01
Gender, n (%)					
Male	24 (62%)	36 (70%)	8 (44%)	8 (40%)	0.3
Female	15 (38%)	15 (30%)	10 (56%)	12 (60%)	
Duration of fever before diagnosis (mean ± SD) / days	7.44 ± 4.52	13.88 ± 11.34	N/A	NA	N/A
WBC count, × 10⁹/L	13.7 (± 5.6)	17.3 (± 15.0)	NA	NA	0.1
Platelet count, × 10⁹/L	394 (± 153)	750 (± 798)	NA	NA	0.008
Hemoglobin, mg/dL	10.9 (± 1.0)	10.1 (± 1.2)	NA	NA	0.002
CRP, mg/dL	101.8 (± 68.5)	65.7 (± 55.5)	NA	NA	0.007
ESR, mm/h	67.7 (± 27.5)	72.7 (± 35.2)	NA	NA	0.5
ALT, IU/L	73.0 (± 85.1)	30.0 (± 34.9)	NA	NA	0.002
AST, IU/L	47.5 (± 54.5)	38.8 (± 51.1)	NA	NA	0.4
ALP	537.4 (± 270.0)	368.5 (± 120.5)	NA	NA	< 0.001
Serum Alb	3.9 (± 0.4)	3.9 (± 0.6)	NA	NA	0.7
cTnI, ng/ml	0.20 (± 0.12)	0.21 (± 0.14)	0.13 (± 0.05)	0.13 (± 0.02)	0.008
cTnT, pg/ml	15.00 (± 22.7)	19.0 (± 27.8)	3.3 (± 1.1)	3.7 (± 1.2)	0.1
CPK-MB, IU/L	21.7 (± 9.4)	27.70 (± 15.8)	22.1 (± 6.7)	26.6 (± 11.6)	0.09

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; ALT: alanine aminotransferase, AST: aspartate aminotransferase; ALP: alkaline phosphatase; Alb: albumin; cTnI: cardiac troponin I; cTnT: cardiac troponin T; CPK-MB: creatine kinase-MB; NA: not available

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Table 2 Comparison of cTnI, cTnT and CPK-MB as cardiac biomarkers of subclinical myocarditis in Kawasaki disease vs. control groups

Cardiac biomarkers	Kawasaki (*n* = 90)	Control (*n* = 38)	*P*. Value	95% Confidence Interval
cTnI, ng/ml	0.23 ± 0.03	0.13 ± 0.04	0.001	0.03_0.12
cTnT, pg/ml	17.24 ± 2.56	3.53 ± 1.15	0.002	5.3_22.1
CPK-MB, IU/L	24.50 ± 13.89	24.62 ± 9.85	0.9	-4.7_5.4

cTnI: cardiac troponin I; cTnT: cardiac troponin T; CPK-MB: Creatine kinase-MB

Table 3 Comparison of cTnI, cTnT and CPK-MB as cardiac biomarkers of subclinical myocarditis in complete vs. incomplete Kawasaki

Cardiac biomarkers	Complete Kawasaki (*n* = 39)	Incomplete Kawasaki (*n* = 51)	*P*. Value	95% Confidence Interval
cTnI, ng/ml	0.20 (± 0.12)	0.21 (± 0.14)	0.9	_0.06_0.05
cTnT, pg/ml	15.00 (± 22.7)	19.0 (± 27.8)	0.5	-15.0_7.1
CPK-MB, IU/L	21.7 (± 9.4)	27.70 (± 15.8)	0.35	-12.4_0.5

cTnI: cardiac troponin I; cTnT: cardiac troponin T; CPK-MB: Creatine kinase-MB

Table 4 Comparison of cTnI, cTnT and CPK-MB in patients with abnormal vs. normal echocardiography

Cardiac biomarkers	Abnormal echocardiography (*n* = 37)	Normal echocardiography (*n* = 53)	*P*. Value	95% Confidence Interval
cTnI, ng/ml	0.23 ± 0.03	0.19 ± 0.02	0.2	_0.02_0.09
cTnT, pg/ml	13.33 ± 2.11	19.88 ± 4.36	0.2	-17.7_4.6
CPK-MB, IU/L	30.42 ± 3.41	21.30 ± 0.96	0.003	3.1_15.1

cTnI: cardiac troponin I; cTnT: cardiac troponin T; CPK-MB: Creatine kinase-MB

Table 5 Comparison of cTnI, cTnT and CPK-MB in patients with transient vs. persistent abnormal echocardiography

Cardiac biomarkers	Transient abnormal echocardiography (*n* = 15)	Persistent abnormal echocardiography (*n* = 16)	*P*. Value	95% Confidence Interval
cTnI, ng/ml	0.24 ± 0.04	0.23 ± 0.02	0.8	_0.09_0.11
cTnT, pg/ml	11.67 ± 2.65	15.54 ± 3.47	0.4	-12.6_4.9
CPK-MB, IU/L	30.50 ± 5.18	30.32 ± 4.27	0.9	-14.1_14.4

cTnI: cardiac troponin I; cTnT: cardiac troponin T; CPK-MB: Creatine kinase-MB

KD (Table 3), febrile controls and healthy controls. Based on the laboratory cutoff level for CK-MB (25 IU/L), 85% of patients with complete KD, 94% with incomplete KD and 55% of control groups had increased CK-MB levels. Anyone patients with increased cardiac biomarkers did not have clinical symptoms of myocarditis.

There was no relationship between cTnI and cTnT levels and the presence of CAI on the first, second and third echocardiograms. However, CK-MB was significantly higher in patients with abnormal echocardiography (Table 4). There was also no significant association between the course of echocardiographic changes throughout the study and the serum level of cardiac biomarkers (Table 5).

The sensitivity, specificity, positive predictive value and negative predictive values of CK-MB, cTnI and cTnT for predicting the occurrence of CAI were determined. Based on the laboratory cutoff for each marker, cardiac troponins have low sensitivity and high specificity for diagnosing CAI in KD. On the other hand, CK-MB had high sensitivity and low specificity in

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predicting CAI (Table 6). All cardiac biomarkers had acceptable negative predictive value for CAI in KD.

Discussion

KD is a systemic vasculitis of unknown origin, primarily seen in the pediatric population (Agarwal and Agrawal 2017; Rowley 2018). Cardiovascular complications, particularly CAI, are known as the main cause of morbidity and mortality in KD (Duarte et al. 2010). Factors such as younger age, late IVIG treatment, higher total neutrophil count and increased platelet count have been found to predict the occurrence of CAI by previous studies (Supachokchaiwattana and Vibulwatanakij 2014; Hamza et al. 2017). It has been suggested that KD-associated myocarditis is associated with coronary artery lesions (Lega et al. 2013).

Despite being known as the earliest and the most common pathological feature of KD, many cases of myocarditis are subclinical and, as a result, not diagnosed by routine investigations (Dionne and Dahdah 2018). Protein biomarkers of cardiomyocyte strain and damage have been used to predict and monitor response to treatment in ischemic heart disease (Wang et al. 2017). Cardiac troponins, particularly cTnI, are more specific and sensitive than CK-MB in detecting myocardial damage (Safford et al. 2013). It has been suggested that sub-clinical myocarditis can be diagnosed by measuring serum levels of myocardial damage markers (Kim and Kim 1999; Checchia et al. 2001).

The present study showed that cardiac troponin levels were significantly increased in KD patients compared to control subjects (Table 2). However, elevated serum cTnI(>0.3 ng/mL) and cTnT(>25 pg/ml) levels were respectively observed in only 15.5% and 10% of KD patients. Checchia et al. measured cTnI levels in children with KD and non-KD controls. Although patients had increased serum cTnI levels compared to controls, the mean value of cTnI was less than that of cardiac damage (Checchia et al. 2001). Moreover, in a study by Yun, cTnT and cTnI levels were significantly elevated in the

KD patients compared to controls; however, the level of cardiac biomarkers did not exceed the normal limit (Yun 2004). Based on these findings, it can be hypothesized that myocytes are not damaged enough during acute KD to release sufficient quantities of cTnI. Another explanation is that manifestations of KD-associated myocarditis are caused by circulating systemic toxins or inflammatory mediators and not myocardiocyte damage (Checchia et al. 2001).

Although the CK-MB isoenzyme is found mainly in the myocardium, it is less sensitive than cTnI and cTnT specific in detecting myocardial injury (Kemp et al. 2004). In our study, CK-MB level was not significantly different between KD patients and controls (Table 2). We observed elevated levels of serum CK-MB (>25 IU/L) in 90% of KD patients, 60% of healthy controls and 50% of febrile controls. Our findings differed from Kim and Kim's, who reported increased CK-MB levels in KD patients (Kim and Kim 1999), which might be explained by the different cut of points used by laboratories.

According to our results, there was no significant relationship between cTnI and cTnT levels and the presence of CAI on each echocardiogram and the course of the disease; however, CK-MB had a higher level in KD with echocardiography abnormalities. Checchia et al. found no correlation between cTnI values and subsequent coronary artery lesions, a finding also reported by Kim et al. (Kim and Kim 1999; Checchia et al. 2001). Similarly, Yun reported only a non-significant increase in CK-MB and cTnI levels in patients with coronary abnormalities compared to other KD patients (Wang et al. 2017). Based on these results, subclinical myocarditis (recognized by elevated cardiac biomarkers) during the acute phase of KD cannot predict subsequent coronary lesions in KD patients. This is further supported by the fact that clinical, electrocardiographic and echocardiographic manifestations of myocarditis, such as left ventricular dysfunction and electrocardiographic changes, have also been found to be unrelated to coronary artery abnormalities (Hematian et al. 2015; Hiraishi et al. 1981; Newburger et al. 1989).

Although cardiac biomarkers did not have a prognosticate value for CAI in our study, they have an excellent negative predictive value. In other words, CAI is unlikely in patients with KD and normal cardiac biomarkers.

Because our center is a tertiary children's medical center with a subspecialty of rheumatology division, patients with the diagnostic challenges of KD refer to our center. So, the frequency of incomplete Kawasaki and abnormal echocardiography was higher than in other studies. A multicenter study with a higher sample size of complete KD is recommended in another study. This study evaluates cardiac biomarkers on the first day

Table 6 The accuracy of the current cut-off values of cTnI, cTnT and CPK-MB as markers of subclinical myocarditis for prediction of CAI in KD

Parameter	cTnI	cTnT	CPK-MB
Sensitivity	15%	8%	91%
Specificity	85%	91%	10%
Positive predictive value	32%	29%	28%
Negative predictive value	70%	70%	74%

cTnI, cardiac troponin I; cTnT, cardiac troponin T; CPK-MB, Creatine kinase-MB; CAI, coronary artery involvement, KD, Kawasaki disease

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of diagnosis and repeated evaluation of these biomarkers (after two weeks) suggests future studies.

Conclusions

It can be concluded that subclinical myocarditis occurs during KD, and serum cTnI and cTnT levels significantly elevate during KD. However, there is no significant association with subsequent CAI based on serial echocardiography. Cardiac troponins have low sensitivity and high specificity, and CK-MB had high sensitivity and low specificity for predicting CAI in KD. Anyone cardiac biomarkers cannot predict persistent CAI, but all cardiac biomarkers have acceptable negative predictive values for CAI in KD.

Abbreviations

KD: Kawasaki disease; CAI: Coronary arterial involvement; cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; CK: Creatine kinase.

Author contributions

M.M. and S.R performed data gathering and drafting of the manuscript and analyzed and interpreted the clinical data. Y.A., M.H.M and F.T. contributed to the conception and design of the study and clinical expertise. E.M. performed echocardiography and contributed to interpretation of the clinical data.
V.Z. provided the concept the survey and interpretation of the clinical data, oversaw the project and critical revision of the final draft of manuscript and primary responsibility for the paper. All authors read and approved the final version of the manuscript.

Availability of data and materials

Requests for access to the data, which gathered and analyzed during the current study are available from the corresponding author, V.Z.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Tehran University of Medical Sciences.

Consent for publication

Written consent has been obtained from all guardian of patient. The author for correspondence is in possession of this document.

Competing interests

The authors declare that they have no competing interests.

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