CARDIAC TROPONIN-T IN ACUTE RHEUMATIC FEVER

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ABSTRACT

Objective: Acute rheumatic fever is still one of the leading causes of mortality and morbidity due to heart disease in developing countries. Carditis is the most important manifestation of the disease and there are still difficulties in diagnosis. Cardiac troponin-T measurement has been found to be valuable in recognition of cardiac injury in various disease states. We investigated the cardiac troponin-T levels in patients with acute rheumatic fever and searched for a difference between patients with and without carditis.

Methods: The study group consisted of 21 patients; 12 were girls and 9 were boys. Their age ranged between 6-16.5 years (mean±SD=11.9±2.5 yrs). Seven patients had only arthritis; 10 patients had both carditis and arthritis; and 4 patients had chorea as clinical diagnosis. Echocardiographic examination showed aortic and mitral regurgitation in 7, mitral regurgitation in 8 and aortic regurgitation in one patient. Serum levels of creatin phosphokinase (CK) and MB (CK-MB) fraction and cardiac troponin-T were measured during the diagnosis before the initiation of treatment in all patients. None of the patients had clinically overt congestive heart failure.

Results: It was observed that CK and CK-MB levels were increased in one patient with carditis and arthritis while cardiac troponin-T levels were below the measurable levels in all patients.

Conclusion: We concluded that cardiac troponin-T measurement has no value in detecting the presence of carditis in rheumatic fever. This may result from absence of myocardial necrosis despite the presence of intense myocardial inflammation.

Key Words: Troponin, Rheumatic fever, Carditis, Echocardiography

INTRODUCTION

Acute rheumatic fever (ARF) is still prevalent and one of the leading causes of mortality and morbidity due to acquired heart disease in developing countries (1). The Jones criteria described by T. Duckett Jones in 1944; revised in 1962 and updated in 1992 is the only method for clinical diagnosis (2, 3). Although these criteria provide easy clinical judgement; there are some difficult cases in which clear cut diagnosis is not possible (4). A laboratory test specific for the disease has not yet been found. Carditis is the most important manifestation for long term prognosis. The presence of carditis is diagnosed by auscultation findings and this may not be accurate enough. Echocardiographic examination in all patients with rheumatic fever may provide better decision making, but this may not be possible, especially in the underprivileged regions of developing countries.

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Cardiac troponins are structural proteins that take place in actin myosin complex and play a role in myocardial contraction. The troponin molecule has three components: cardiac troponin-T (cTN-T) is the tropomyosine binding part, cardiac troponin-I (cTN-I) is the inhibitor part and cardiac troponin-C (cTN-C) is the calcium binding part (6). These proteins are found in the serum of patients after myocardial cell injury. Since the troponins in the skeletal and cardiac muscle cells have different molecular structures, the measurement of serum cardiac troponin levels gives specific information about myocardial necrosis (6). Troponin-T and troponin-I are routinely used in adult patients with acute coronary syndromes and they are found to be more specific than creatin kinase and MB isoenzyme, previously used as biochemical markers of myocardial injury (6, 7). Serum troponin-T levels are also found to be elevated in patients with myocarditis (8).

Carditis of rheumatic fever is a pancarditis and involves the three layers of the heart including the myocardium (9). If a marker of myocardial involvement was found, it would be quite helpful for the management and follow-up of these patients. We considered whether troponin-T could provide such information and investigated the serum level of troponin-T in patients with ARF with and without carditis.

MATERIALS AND METHODS

The study group consisted of all patients diagnosed with acute rheumatic fever according to Jones criteria in the Marmara University School of Medicine, Pediatric Cardiology Sub-department, between January 1998 and December 1999.

After detailed history taking and physical examination, a telecardiogram, electrocardiogram, complete blood count, erythrocyte sedimentation rate, C-reactive protein, throat culture and antistreptolysine - O titers were obtained in all patients. Serum creatin kinase (CK) and creatin kinase MB fraction were measured and serum samples were separated and frozen at - 70°C during diagnosis before the initiation of antiinflammatory treatment.

All the patients underwent echocardiographic examination. Echocardiography was performed by using ATL Ultramark 9 machine equipped with 2.5, 3.5 and 5 MHz transducers.

The presence of carditis was determined on clinical grounds, by auscultation of a new onset murmur suggestive of mitral or aortic regurgitation and/or pericardial friction rub or clinical evidence of heart failure. Patients with echocardiographic evidence of mitral regurgitation without auscultation findings were not accepted as having active carditis.

Serum troponin-T levels were measured after collection of a sufficient number of serum samples by using Elecsys Boehringer Mannheim ELISA kit and Elecsys 1010 analyser.

Serum samples were also taken from the healthy children evaluated for non-cardiac disease while drawing blood for routine test as a control group, and measurements were performed at the same time.

Troponin-T levels of the patients with and without carditis and the control group were compared. CK and CK-MB levels of the patients with and without carditis were compared by using Mann-Witney U test.

RESULTS

The study group included 21 patients. Twelve of them were girls and 9 of them were boys. Their ages ranged between 6 and 16.5 years (mean ± SD = 11.9 ± 2.5 yrs). All the patients had their first attack of rheumatic fever, none of them had a previous history of arthritis or carditis. The control group consisted of 5 girls and 5 boys between the ages of 5 and 16 years (mean ± SD = 11.4 ± 3.5).

Seven patients had only arthritis as a major manifestation, 10 patients had both arthritis and carditis (previously healthy children with initial attack of active carditis with new onset murmur of mitral regurgitation and elevated acute phase reactants associated with overt clinical symptoms of arthritis), and 4 patients were presented with chorea. None of the patients with carditis had clinical signs of congestive

heart failure. Antistreptolysine – O titers were elevated in all patients except two with chorea. Erythrocyte sedimentation rate ranged between 9 to 14 mm/hour (mean ± SD = 70.2 ± 41.3 mm/h). PR interval ranged between 0.12 to 0.28 seconds (mean ± SD = 0.15 ± 0.04 sec).

Echocardiographic examination revealed both mitral and aortic regurgitation in seven patients, only mitral regurgitation in eight patients and only aortic regurgitation in one patient. In five patients, echocardiographic examination was normal without any valvular involvement. All patients with chorea had mild mitral regurgitation and two patients diagnosed to have only arthritis by clinical judgement also had mild mitral regurgitation. The mild mitral regurgitation found in patients without clinical carditis was not consistent with the physiologic trivial mitral regurgitation that can be found in normal individuals.

Serum CK and CK-MB levels were elevated in only one patient with carditis and arthritis. (CK = 302 U/L and CK-MB = 46 U/L) and in one patient with arthritis only CK was elevated (348 U/L). Serum CK levels ranged between 13 and 348 U/L; and CK-MB levels ranged between 0 and 46/U/L. There was no statistically significant difference between the patients with carditis and without carditis in terms of CK and CK-MB levels. The serum cardiac troponin T levels were found to be under the measurable level (<0.01 ng/dl) in all subjects with or without carditis and the control group.

The summary of CK, CK-MB and Troponin T levels according to clinical involvement of the patients are given in the table I.

DISCUSSION

Acute rheumatic fever is still the most important cause of acquired heart disease in developing countries. Although its incidence and severity has decreased in developed countries it is not entirely eradicated and may cause cardiac morbidity (10). The diagnosis of acute rheumatic fever is possible only on clinical grounds by using Jones criteria, no clinical or laboratory test pathognomonic for the disease has been found up to date (11). The Jones criteria has been revised and updated several times in order to increase sensitivity ad specificity, these criteria are quite helpful to the practitioners for decision making but there are some difficult cases in which clear cut diagnosis may be a problem (3, 4).

Carditis is the most important major criteria of ARF since it is the only one that causes permanent damage (12). It is found in up to 30-50 % of patients with ARF. The presence of carditis is determined by auscultation of apical systolic and/or basal diastolic murmurs, clinical diagnosis of pericarditis or unexplained congestive heart failure (12). However, echocardiographic findings are not always consistent with the clinical findings. Even experienced physicians may not detect valvular regurgitation during routine examination. Mitral regurgitation found in acute rheumatic fever is due to ventricular dilatation or restriction of the leaflet mobility in most of the cases and may disappear or decrease in severity during the follow-up (5). Various studies have demonstrated that many patients considered to have isolated arthritis or chorea had echocardiographic

Table I.: CK, CK-MB- Troponin T levels of the patients according to their clinical involvement.

Clinical manifestation	N (years)	Age (M/F)	Gender (N: 5-130) (N:0-26)	CK (U/L) MB (U/L)	CK- (ng/dl)	Troponin T
Arthritis	7	11.3±2.9	2/3	193.0±219.2	20.5±0.7	<0.01
Arthritis+Carditis	10	11.8±2.5	5/5	107.0±108.8	9.5±12.0	<0.01
Chorea	4	12.6±1.7	2/2	87.0±65.1	21.5±3.5	<0.01
Total	21	11.9±2.5	9/12	101.4±93.8	14.1±11.9	<0.01
Control group	10	11.4±3.5	5/5	–	–	<0.01

evidence of valvular involvement (12-14). We also found a similar result in our patients; four patients with chorea and two patients with isolated arthritis had mild mitral regurgitation revealed by echocardiograhy. It is harder to recognize a new attack in a patient with previous valvular disease. Although one may consider performing echocardiography in all patients with suspected ARF, it is not cost-effective and echocardiography may not be available in the rural areas of developing countries. Furthermore, echocardiography also has some pitfalls such as differentiation of physiologic mitral regurgitation (15).

Thus, a biochemical marker specific for carditis would provide invaluable information for straightforward diagnosis of ARF in difficult cases. Cardiac troponin-T and troponin-I are found to be specific for myocardial cell injury in various disease states (16). They are also studied in pediatric age group and found to be elevated in myocardial necrosis due to trauma, cardiac surgery, neonatal ischemia, myocarditis and anthrayclin toxicity (17-21). However, our study demonstrated that no such increase in serum cardiac troponin-T levels occurs in patients with ARF even in the presence of carditis. Narula et al (22) have studied scintigraphic imaging of antimyosin antibodies for detection of carditis in patients with ARF and they could obtain a high degree of scintigraphic uptake only in patients with pericarditis and severe congestive heart failure. They concluded that this finding is due to the lack of myocardial cell necrosis in the carditis of ARF. Possibly it holds true for troponin-T measurements and rheumatic carditis does not cause troponin-T elevation since myocardial necrosis does not occur despite intensive inflammation in ARF. The clinical evidence of myocarditis is tachycardia or congestive heart failure, however; neither myocarditis nor pericarditis is considered as rheumatic carditis when valvular involvement is not present. Histologic findings specific for rheumatic myocarditis is Aschoff nodules and histiocyte infiltration but Narula et al (23) has found these typical findings in only 27% of the patients who had clearcut diagnosis of active rheumatic carditis according to revised Jones criteria. Some authors suggest that the term myocarditis is not appropriate for rheumatic myocarditis when Dallas criteria are used, since distinctive findings of myocyte necrosis and associated lymphocyte infiltration is absent (23). In all other patients with myocardial injury due to for example ischemia, viral myocarditis, trauma or surgery, there is myocardial cell necrosis causing the release of intracellular ingredients, including cardiac troponins, into the circulation. Left ventricular functions are preserved even during the acute phase of the disease and decreased left ventricular shortening fraction is thought to be due to valvular lesions when present. This also indicates that acute rheumatic fever is an inflammatory disease rather than a degenerative one (5). Permanent sequela of ARF is due to endocardial damage healing with fibrosis, not to the myocardial necrosis. Our study group did not include patients with congestive heart failure and pericarditis in which troponin elevation would be a non-specific finding as previous studies have demonstrated (24). On the other hand, the number of the patients included is limited and this may be the cause of the negative result.

In conclusion, serum troponin-T level does not increase and is not beneficial in the diagnosis and follow-up of rheumatic carditis. Further investigation is necessary for assessment of the value of troponin measurements in childhood.

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REFERENCES

1. *Bitar FF, Hayek P, Gharzeddine W, Mikati M, Dbaibo GS. Rheumatic fever in children: A 15-year experience in a developing country. Pediatr Cardiol 2000;21:119-122.*
2. *Mirkinson L. The diagnosis of rheumatic fever. Pediatrics in review 1998;19:310-311.*
3. *Special writing committee on rheumatic fever, endocarditis and Kawasaki Disease of the council on cardiovascular disease in the*

young of the American Heart Association. Guidelines for the diagnosis of rheumatic fever. JAMA 1992;268:2069-2073.

4. Williamson L, Bowness P, Mowat A, Östman-Smith I. Difficulties in diagnosing acute rheumatic fever-arthritis may be short lived and carditis silent. Br Med J 2000;320:362-365.
5. Vasan RS, Shirivastava S, Vijayakumar M, Narag R, Lister B, Narula J. Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. Circulation 1996;94:73-82.
6. Collinson PO. Troponin T or Troponin I or CK-MB (or none?). Eur Heart J 1998;19 (suppl N): N16-N24.
7. Hetland O, Dickstein K. Cardiac troponins I and T in patients with suspected acute coronary syndrome: a comparative study in routine setting. Clin Chem 1998;44:1430-1436.
8. Lauer B, Niederau C, Kühl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. J Am Coll Cardiol 1997;30:1354-1359.
9. El-Said GM, El-Refaee MM, Sorour KA, El-Said HG. Rheumatic fever and rheumatic heart disease. In: Garson A, Bricker JT, Fisher DJ, Neish SR. eds. The science and practice of pediatric cardiology, 2nd edn. Baltimore, Williams and Wilkins, 1998:1691-1724.
10. Kaplan E. Global assessment of rheumatic fever and rheumatic heart disease at the close of century. Circulation 1993;88:1964-1972.
11. Veasy LG. Rheumatic fever - T. Duckett Jones and the rest of the story. Cardiol Young 1995;5:293-301.
12. Narula J, Chandrasekhar Y, Rahimtoola S. Diagnosis of active rheumatic carditis. Circulation 1999;100:1576-1581.
13. Veasy LG, Wiedmeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. N Eng J Med 1987;316:421-427.
14. Veasy LG, Tani LY, Hill HR. Persistence of acute rheumatic fever in the intermountain area of the united states. J Pediatr 1994;125:673-674.
15. Brand A, Dollberg S, Keren A. The prevelance of valvular regurgitation in children with structurally normal hearts: a color Doppler echocardiographic study. Am Heart J 1992;123:177-180.
16. Lipshultz SE, Rifai N, Sallan SE, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997;96:2641-2648.
17. Hirch R, Landt Y, Porter S. et al. Cardiac troponin I in pediatrics: normal values and potential use in the assessment of cardiac injury. J Pediatr 1997;130:872-877.
18. Immer FF, Stocker FP, Seiler AM, Pfammatter JP, Printzen G, Carrel TP. Comparison of troponin I and troponin T after pediatric cardiovascular operation. Ann Thorac Surg 1998;66:2073-2077.
19. Panteghini M, Agnoletti G, Pagani F, Spandrio M. Cardiac troponin T in serum as a marker for myocardial injury in newborns. Clin Chem 1997;43:1455-1457.
20. Kim M, Kim K. Elevation of cardiac troponin I in the acute stage of Kawasaki Disease. Pediatr Cardiol 1999;20:184-188.
21. Fink FM, Genser N, Fink C, et al. Cardiac troponin-T and creatine Kinase MB mass concentrations in children receiving anthrocycline chemotheraphy. Med Pediatr Oncol 1995;25:185-189.
22. Narula J, Malhotra A, Yasuda T. Usefulness of antimyosin antibody imaging for the detection of active rheumatic myocarditis. Am J Cardiol 1999;84:946-950.
23. Narula J, Chopra P, Talwar KK et al. Does endomyocardial biopsy aid in the diagnosis of active rheumatic carditis? Circulation 1993;88:2198-2205.
24. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive heart failure. Circulation 1997;96:2953-2958.