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Oxidative Stress of Kawasaki Disease: Comparison between Acute and Convalescent Phase along with Administration of IVIG

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Abstract

Background: Kawasaki disease (KD) is common disease in infancy and early childhood in Japan. Association KD with oxidative stress has been reported, whereas many diseases are associated with oxidative stress.

Objects: This study investigated the association KD and oxidative stress.

Subjects and Method: We evaluated serum oxidative stress marker as D-ROMs, derivatives of reactive oxygen metabolites, on acute and convalescent phase of KD and compared the value on two phases.

Results: The mean levels of D-ROMs was 576.2 ± 86.2 U.CARR on acute phase, and that on convalescent phase was 535.2 ± 85.0 U.CARR. The levels were significantly reduced after IVIG therapy (p = 0.030).

Conclusion: Kawasaki disease is a systemic vasculitis and is important with regard to the complication of coronary artery lesions. Oxidative stress could affect the vascular lesion in KD.

Keywords: Kawasaki disease; Oxidative stress; D-ROMs

Introduction

It has been described that many diseases are associated with oxidative stress and several biomarkers reflecting with oxidative stress are available. However, few reported association of Kawasaki disease and oxidative stress. Therefore, we evaluated serum oxidative stress marker, using simpler method of hydroperoxides (ROOH) levels by measuring derivatives of reactive oxygen metabolites (D-ROMs) [1], on acute and convalescent phase of Kawasaki disease.

Subjects and Methods

The subjects were 14 patients (male : female 8:6), of Kawasaki disease admitted to Yokohama City Minato Red Cross Hospital from January 2008 to March 2009, whose mean age was 34.3 ± 22.2 months of age. The detail of subjects is presented in Table 1. D-ROMs were measured (d-ROMs test; Diacron, Grosseto, Italy) before administration of intravenous immune globulin (IVIG) acute and about 7days after IVIG therapy convalescent phase. All patients were administered IVIG (2g/kg). We analyzed these data retrospectively. We compared the values in acute and convalescent phase. Additionally, correlations between the value of D-ROMs and those of white blood cell counts, platelet counts, C reactive protein and aspartate amino transferase in acute phase were calculated.

	pre IVIG	post I VIG	*p* value
n	14		
male, sex (%)	8 (57.1%)		
age (mo/o)	34.3 (12~76, 26)		
white blood cell counts (×10^3/μL)	12.75±2.59	7.59±2.15	< 0.001
peripheral neutrophils counts (/μL)	7.09±2.50	2.11±0.77	0.008
platelets counts (×10^3/μL)	30.0±4.9	42.7±10.5	0.010
C reactive protein (mg/dl)	9.79±4.36	2.76±5.17	0.007
serum albumin	3.65±0.25	3.65±0.25	NS
aspartate amino transferase (U/L)	122.4±127.4	50.6±30.9	NS
alanine aminotransferase (U/L)	129.3±139.5	38.0±29.1	NS
periods of administration of IVIG from onset (days)	4.9±0.9		
complication of coronary lesion	1 (7.1%)		
transient mild dilatation	1 (7.1%)		
aneurytm	0 (0%)		

The data shows mean ± *SD* or number (%). NS; not significant.

Table 1: Characteristics of subjects.

Data were statistically analyzed by Wilcoxon signed-rank test and Spearman rank correlation coefficient using SPSS ver. 16 (IBM, CO., LTD., Japan). *P* values < 0.05 were considered significant.

Results

The mean levels of D-ROMs was 576.2 ± 86.2 U.CARR on acute phase, and that on convalescent phase was 535.2 ± 85.0 U.CARR. The levels were significantly reduced after IVIG therapy (p = 0.030) (Figure 1). The value of D-ROMs did not correlated with those of white blood cell counts, platelet counts, C reactive protein and aspartate amino transferase in acute phase (Table 2).

Discussion

There have been no reports of oxidative stress in association with Kawasaki disease with few exceptions. Takeuchi et al. [2] described urinary 8-isoprostane, one of oxidative stress markers, of the patients

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of acute Kawasaki disease were higher than that of controlled subjects. Takatsuki et al. [3] described that urinary 8-iso-prostaglandin reduced after 7 days initiated IVIG therapy and concluded that oxidative stress provokes vasculitis in Kawasaki diseases, the activation of which was reduced by IVIG and the urinary 8-iso-prostaglandine is a useful marker for the effectiveness of IVIG in the acute phase of Kawasaki disease. Our data encourage their description from the perspective of D-ROMs directly reflecting serum oxidative stress. Furthermore D-ROMs is also a useful, more convenient marker for the effectiveness of IVIG in the acute phase of Kawasaki disease. Additionally, Cheung et al. [4] described that the patients of Kawasaki disease complicated with coronary aneurysms had significantly higher serum levels of malonaldehyde and hydroperoxides. Interestingly oxidative stress is associated with atherosclerosis, the lesion of artery. Kamezaki et al. [5] described oxidative stress increases in patients at high risk for cardiovascular events on their high-sensitivity protein (hsCRP) by means of measurement of D-ROMs.

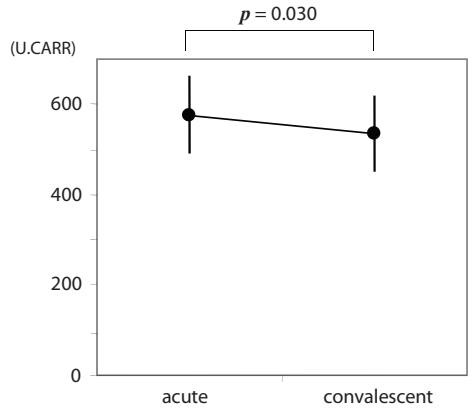
The number of subjects in our study was too small, there were not patient permanent coronary lesions, excluding a case of transient mild dilatation of coronary artery. However, we estimated that D-ROMs could be a prospective marker of coronary artery lesions, because D-ROMs was also serum oxidative marker as same such as malonaldehyde and hydroperoxides. Moreover, our data suggested that the value of D-ROMs did not correlated with those of white blood cell counts, platelet counts, C reactive protein and aspartate amino transferase in acute phase. D-ROMs could have another meaning than exisiting examinations in KD.

	WBC	Plt	CRP	AST
D-ROMs	0.3817	-0.047	0.0324	0.0459
	p=0.1660	p=0.8761	p=0.9125	p=0.8761

WBC; white blood cell counts, Plt; platelet counts, CRP; C reactive protein, AST; aspartate amino transferase

Data are revealed coefficient ρ in upper line and p value in lower line.

Table 2: Correlations between the value of D-ROMs and those of white blood cell counts, platelet counts, C reactive protein and aspartate amino transferase in acute phase.



Dots represent mean values of D-ROMs and bars represent standard deviations. The levels of D-ROMs were significantly reduced after IVIG therapy (p = 0.030, Wilcoxon's signed rank test).

Figure 1: Change of D-ROMs after IVIG administration.

There has been some evidence that suggests the involvement of oxidative stress in the pathophysiology of vasculitis. Ames et al. [6] reported that plasma 8-epi- prostaglandin α levels were high in patients with systemic lupus erythema, systemic sclerosis and vasuculitis and 8-epi- prostaglandin α concentration correlated with disease activity in Wargener' granulomatosis and Churge Strauss syndrome. They concluded that oxidative stress may be pathogenically relevant in rheumatic disease with vasucular involvement. Ece et al. [7] reported that active stage of Henoch-Scholein purpula had significant higher serum malondialdehyde reflecting with oxidative stress and lower serum total anioxidant status.

Wu et al. [8] described that antioxidants inhibited early vusculitis in vivo on animal model. The effectiveness of IVIG in vasculitis other than KD is not evident, because those have not been reported. However, oxidative stress is generally reduced by adequate therapy and correlate with disease activity in several vasculitis syndromes, similar to our patients with Kawasaki disease.

Kishimoto et al. [9] reported that high dose IVIG therapy reduced plasma level of thioredoxin in patients with acute inflammatory myocardiopathy and concluded that IVIG therapy may suppress not only inflammatory cytokines but also oxidative stress. IVIG in our cases of Kawasaki disease may reduce oxidative stress similar to that report.

Kawasaki disease is a systemic vasculitis and is important with regard to the complication of coronary artery lesions. Further study is needed to elucidate how oxidative stress affected and coronary artery lesions on acute phase of Kawasaki disease.

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