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ORIGINAL ARTICLE

Comparison of the Laboratory Data Between Kawasaki Disease and Enterovirus After Intravenous Immunoglobulin Treatment

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Abstract Kawasaki disease (KD) is a systemic vasculitis of unknown etiology. The laboratory findings before and after intravenous immunoglobulin (IVIG) in KD have been discussed, but the characteristics of IVIG therapy still are unclear. This study aimed to compare laboratory data from patients with KD and enterovirus (EV) infection to evaluate the differences after IVIG therapy. The study enrolled 171 KD patients and 38 EV patients treated with a single dose of IVIG from 2003 to 2010. Laboratory data including total white blood cell counts (WBC) and hemoglobin (Hb), platelet, segment, lymphocyte, eosinophil, and monocyte levels were analyzed. Compared with the KD patients, the EV patients had higher Hb, lymphocyte, and monocyte levels and lower eosinophil levels before IVIG treatment ($p < 0.05$). After IVIG treatment, the KD patients had lower Hb and segment levels but higher platelet, lymphocyte, and eosinophil levels than the EV patients ($p < 0.05$). In the KD patients, the platelet, eosinophil, and monocyte levels increased after IVIG treatment, whereas Hb, WBC, and segment levels decreased significantly ($p < 0.001$). In the EV patients, eosinophil levels increased after IVIG treatment, whereas WBC and Hb levels decreased significantly ($p < 0.05$). The study results provide evidence that eosinophilia may be related to IVIG therapy in KD and EV patients. The KD patients had higher eosinophil levels both before and after IVIG therapy than the EV patients, which may have been due to the inflammatory mechanism of KD. The KD patients had higher platelet levels than the EV patients, suggesting that platelets are involved in the inflammatory response to KD.

Keywords Enterovirus · Eosinophil · IVIG · Kawasaki disease

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Kawasaki disease (KD) is an acute multisystemic vasculitis syndrome of unknown etiology that occurs mainly in children younger than 5 years of age. It was first reported in English by Dr. Tomisaki Kawasaki [8] in 1974.

The clinical characteristics of KD are prolonged fever, nonpurulent conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, and indurative edema of the hands and feet associated with subsequent peeling of the finger tips, and nonsuppurative cervical lymphadenopathy [1, 24]. When patients have a fever lasting more than 5 days and meet four of the five principal criteria for KD, the diagnosis of KD is made [11].

The standard treatment for KD is intravenous immunoglobulin (IVIG) (2 g/kg) infusion for 12 h with high-dose aspirin [14–16]. The most serious complication of KD is the

development of coronary artery lesions (CAL) including myocardial infarction, coronary artery dilation, coronary artery aneurysms, and coronary fistula formation [10, 11, 17].

A recent study found that eosinophil levels were significantly more elevated in patients with KD than in age-matched febrile control subjects [15]. The peripheral blood eosinophil level was markedly increased in the acute stage and returned to normal 3 weeks after IVIG treatment. Eosinophil levels generally are highly elevated in the acute stage of KD both before and after IVIG treatment. After IVIG treatment (within 3 days), eosinophilia is found to have an inverse correlation with IVIG resistance in patients with KD. Kuo et al. [12, 13] also found that plasma levels of interleukin (IL)-5 and peripheral blood eosinophils were associated with protection from CAL formation in KD.

Enterovirus (EV)-associated encephalitis is an emerging infectious disease in Taiwan [3]. It is characterized by fever, lymphopenia, herpangina, or hand-foot-and-mouth disease. The major lethal complications are autonomic nervous system (ANS) dysfunction and progressive respiratory failure due to pulmonary edema, pulmonary hemorrhage, and acute respiratory distress syndrome (ARDS) [4]. Acute flaccid paralysis and aseptic meningitis also have been described [22].

Treatment with IVIG (1 g/kg infusion for 12 h in a single infusion) is indicated for patients with brainstem encephalitis defined as myoclonus, ataxia, nystagmus, oculomotor palsies, and bulbar palsy in various combinations with or without neuroimaging evidence [22]. Autonomic nervous system dysregulation is defined as cold sweating, mottled skin, tachycardia, tachypnea, and hypertension. Pulmonary edema is defined as respiratory distress symptoms and signs (tachycardia, tachypnea, rales, and copious frothy sputum) that develop subsequent to ANS dysregulation, with a chest x-ray that shows bilateral pulmonary infiltrates without cardiomegaly [7, 22].

We enrolled EV patients who received IVIG therapy for comparison with the KD patients because those patients were the most common in our population needing IVIG treatment. To the best of our knowledge, the literature has no published comparisons between KD and EV after IVIG treatment. This study therefore aimed to investigate the role of IVIG treatment for patients with KD and EV.

Patients and Methods

We retrospectively analyzed patients in the Kaohsiung Chang Gung Memorial Hospital, Taiwan from 2003 to 2010. Patients were defined as having KD if they had experienced a prolonged fever and at least four of the following five symptoms: conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, indurative edema of the hands and feet associated with subsequent peeling of the finger tips, and nonsuppurative cervical lymphadenopathy [9, 15].

This study enrolled 171 KD patients who had both pre- and post-IVIG laboratory data. They all were treated with a single dose of IVIG (2 g/kg infusion for 12 h). Aspirin also was given at an antiinflammatory dose until the fever subsided, after which a single daily low dose was continued until all signs of inflammation had resolved.

Enterovirus infection was diagnosed by throat virus isolation, and a life-threatening complication was defined as central nervous system involvement (e.g., acute paralytic syndrome, encephalomyelitis) or cardiopulmonary involvement (e.g., myocarditis, pulmonary edema, pulmonary hemorrhage) [22]. A single dose of IVIG (1 g/kg infusion for 12 h) was used to treat 38 patients with EV infections and life-threatening complications. We collected the laboratory data, including total white blood cell (WBC) counts and hemoglobin (Hb), platelet, segment, lymphocyte, eosinophil, and monocyte levels, before IVIG and within 7 days after IVIG therapy. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB no. 100-1120B).

Statistical Analysis

Comparisons of continuous data (mean ± standard deviation) were made using Student's t tests, and comparisons between groups were done using chi-square tests. Changes before and after IVIG treatment were tested by the paired sample t test. A p value less than 0.05 was accepted as statistically significant. All statistical tests were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

The mean age of the KD patients was significantly younger than that of the patients with EV (20.39 ± 1.28 vs. 28.32 ± 4.50 months, $p = 0.02$). The KD and EV patients did not differ significantly with regard to the number of children younger than 12 months. Male gender was found to be significantly more prevalent among the KD patients (117/171, 68 %) than among the EV patients (19/38, 50 %) ($p = 0.03$; Table 1).

Laboratory Data Before IVIG Treatment

Before IVIG therapy, the Hb level of the KD patients was lower than that of the EV patients (10.97 ± 1.32 g/dl vs. 12.53 ± 1.78 g/dl, $p < 0.0001$). The KD patients had a significantly higher percentage of eosinophils than the EV

Table 1 Characteristics of the Kawasaki disease and enterovirus patients

	Kawasaki disease	Enterovirus infection	*p* value[a]
Age (months)	20.39 ± 1.28	28.32 ± 4.50	0.02
Age <12 months (%)	40.9	28.9	0.17
Male gender (%)	68	50	0.03

[a] $p < 0.05$ by chi-square and Student's *t* tests was considered significant

patients (2.72 ± 2.94 % vs. 0.49 ± 0.93 %, $p < 0.0001$) and lower percentages of lymphocytes (24.84 ± 12.83 % vs. 31.07 ± 16.72 %; $p = 0.036$) and monocytes (5.99 ± 3.45 % vs. 7.28 ± 3.62 %; $p = 0.04$) (Table 2).

Laboratory Data After IVIG Treatment

After IVIG therapy, the KD patients had a lower Hb level than the EV patients (10.62 ± 1.18 g/dl vs. 11.65 ± 1.90; $p = 0.003$) and a higher platelet count (45.08 ± 15.96 × 10^4/mm^3 vs. 27.16 ± 12.04 × 10^4/mm^3; $p < 0.001$). They had a higher percentage of eosinophils than the EV patients (4.65 ± 4.46 % vs. 1.78 ± 2.58 %; $p < 0.001$), a lower percentage of neutrophils (40.24 ± 19.07 % vs. 51.59 ± 23.06 %; $p = 0.007$), and a higher percentage of lymphocytes (45.31 ± 18.16 % vs. 36.35 ± 20.98 %; $p = 0.008$) (Table 3).

Laboratory Data of the KD Patients

After IVIG therapy, the KD patients had higher levels of platelets (34.71 ± 11.94 × 10^4/mm^3 vs. 45.02 ± 15.96 × 10^4/mm^3; $p < 0.0001$), eosinophils (2.72 ± 2.94 % vs. 4.65 ± 4.46 %; $p < 0.0001$), and lymphocytes (24.84 ± 12.83 % vs. 45.31 ± 18.16 %; $p < 0.0001$) than before IVIG therapy. However, after IVIG therapy, they had significantly lower levels of Hb (10.97 ± 1.32 g/dl vs. 10.62 ± 1.18 g/dl; $p < 0.0001$), total WBC (13,936.84 ± 4,688.79/mm^3 vs. 9,918.77 ± 3,990.85/mm^3; $p < 0.0001$), and neutrophils (65.19 ± 13.37 % vs. 40.24 ± 19.07 %; $p < 0.0001$) than before IVIG therapy (Table 4).

Laboratory Data of the EV Patients

After IVIG therapy, the EV patients had a significantly decreased Hb level (11.65 ± 1.90 g/dl vs. 12.53 ± 1.78 g/dl; $p = 0.01$) and a higher eosinophil level (0.49 ± 0.93 % vs. 1.78 ± 2.58 %; $p = 0.002$) than before IVIG therapy. Their total WBC count was significantly decreased after IVIG treatment (14,265.79 ± 7,964.42/mm^3 vs. 10,257.89 ± 5,316.35/mm^3; $p = 0.003$). However, there were no significant differences in platelet, neutrophil, or lymphocyte levels before and after IVIG treatment (all $p > 0.05$) (Table 5).

Discussion

In our previous study we found that patients with KD have a higher percentage of eosinophils than control subjects [15]. In addition, post-IVIG eosinophilia (peripheral blood eosinophils, ≥4 %) had an inverse correlation with IVIG resistance in KD patients. Levels of eosinophil-related mediators, IL-4, IL-5, eotaxin, and eosinophil cationic

Table 2 Comparison between Kawasaki disease and enterovirus infection before intravenous immunoglobulin (IVIG) therapy[a]

	Kawasaki disease	Enterovirus infection	*p* value
WBC (cell/mm^3)	13,936.84 ± 4,688.79	14,265.79 ± 7,964.42	0.8
Hb (g/dl)	10.97 ± 1.32	12.53 ± 1.78	<0.0001[b]
Platelet (×10^4/mm^3)	34.71 ± 11.94	31.19 ± 9.03	0.08
Neutrophil (%)	65.19 ± 13.37	59.99 ± 17.87	0.09
Lymphocyte (%)	24.84 ± 12.83	31.07 ± 16.72	0.036[b]
Eosinophil (%)	2.72 ± 2.94	0.49 ± 0.93	<0.0001[b]
Monocyte (%)	5.99 ± 3.45	7.28 ± 3.62	0.04[b]

WBC white blood cell; *Hb* hemoglobin

[a] Values are expressed as mean ± standard deviation

[b] $p < 0.05$, Student's *t* test

Table 3 Comparison between Kawasaki disease and enterovirus infection after intravenous immunoglobulin (IVIG) therapy[a]

	Kawasaki disease	Enterovirus infection	*p* value
WBC (cell/mm^3)	9,918.77 ± 3,990.85	10,257.89 ± 5,316.35	0.6
Hb (g/dl)	10.62 ± 1.18	11.65 ± 1.90	0.003[b]
Platelet (×10^4/mm^3)	45.08 ± 15.96	27.16 ± 12.04	<0.001[b]
Neutrophil (%)	40.24 ± 19.07	51.59 ± 23.06	0.007[b]
Lymphocyte (%)	45.31 ± 18.16	36.35 ± 20.98	0.008[b]
Eosinophil (%)	4.65 ± 4.46	1.78 ± 2.58	<0.001[b]
Monocyte (%)	7.54 ± 3.67	7.31 ± 3.22	0.72

WBC white blood cell; *Hb* hemoglobin

[a] Values are expressed as mean ± standard deviation

[b] $p < 0.05$, Student's *t* test

Table 4 Comparison of Kawasaki disease in before and after intravenous immunoglobulin (IVIG) therapy[a]

	Pre-IVIG	Post-IVIG[b]	*p* value
WBC (cell/mm^3)	13,936.84 ± 4,688.79	9,918.77 ±3,990.85	<0.0001[c]
Hb (g/dl)	10.97 ± 1.32	10.62 ± 1.18	<0.0001[c]
Platelet ($\times 10^4$/mm^3)	34.71 ± 11.94	45.02 ± 15.96	<0.0001[c]
Neutrophil (%)	65.19 ± 13.37	40.24 ± 19.07	<0.0001[c]
Lymphocyte (%)	24.84 ± 12.83	45.31 ± 18.16	<0.0001[c]
Eosinophil (%)	2.72 ± 2.94	4.65 ± 4.46	<0.0001[c]
Monocyte (%)	5.99 ± 3.45	7.54 ± 3.67	<0.0001[c]

WBC white blood cell; *Hb* hemoglobin

[a] Values are expressed as mean ± standard deviation

[b] Within 3 days after the first dose of IVIG treatment

[c] $p < 0.05$, paired-sample *t* test

Table 5 Comparison of enterovirus infection before and after intravenous immunoglobulin (IVIG) therapy[a]

	Pre-IVIG	Post-IVIG[b]	*P* value
WBC (cell/mm^3)	14,265.79 ± 7,964.42	10,257.89 ± 5,316.35	0.003[c]
Hb (g/dl)	12.53 ±1.78	11.65 ± 1.90	0.01[c]
Platelet ($\times 10^4$/mm^3)	31.19 ± 9.03	27.16 ± 12.04	0.129
Neutrophil (%)	59.99 ± 17.87	51.59 ± 23.06	0.069
Lymphocyte (%)	31.07 ± 16.72	36.35 ± 20.98	0.181
Eosinophil (%)	0.49 ± 0.93	1.78 ± 2.58	0.002[c]
Monocyte (%)	7.29 ± 3.62	7.31 ± 3.22	0.97

WBC white blood cell; *Hb* hemoglobin

[a] Values are expressed as mean ± standard deviation

[b] Within 3 days after the first dose of IVIG treatment

[c] $p < 0.05$, paired-sample *t* test

protein (ECP), also were found to be higher in KD patients than in control subjects before IVIG treatment [12]. After IVIG treatment, levels of ECP decreased, but levels of IL-4, IL-5, and eotaxin increased significantly. The lower the IL-5 and eosinophil levels were after IVIG treatment, the higher the rate of CAL that was found [12].

The Th2 cytokines did not differ between KD patients with an allergic disease history and those without such a history. Therefore, it is interesting to consider whether the Th2 immune response (eosinophil, IL-5, IL-4, and eotaxin) results from the IVIG treatment or from the disease course of KD. We hypothesized that eosinophils in KD are a witness of the Th2 immune response due to the eosinophil positivity associated with the Th2 immune response (IL-5) but not with its activation marker (ECP). Moreover, eosinophils also are a witness of disease outcome (CAL formation and IVIG treatment response) in the acute stage and may have some role in the late allergy.

Both EV and KD patients receive high-dose IVIG treatment during the acute phase of their disease. However, there been no reports on eosinophil levels in EV patients nor any comparisons between EV and KD patients. It is important to investigate whether the eosinophilia found in KD may also be found in EV patients after IVIG treatment to distinguish whether eosinophilia is IVIG related or disease related.

A recent report found that allergic diseases (e.g., asthma, allergic rhinitis, allergic conjunctivitis) are more common among patients with KD than among control subjects [18]. Patients with KD have a greater tendency for atopy because an older age is associated with a higher susceptibility to allergies. The patients with EV also had elevated eosinophil levels after IVIG therapy in our study, although the levels were not as high as for the KD patients after IVIG treatment.

The development of allergic diseases or idiopathic thrombocytopenic purpura (ITP, also treated with IVIG) in EV patients has not been studied to date, and the incidences of allergic diseases among KD, EV, and ITP patients need further investigations. In our study, both EV and KD patients had elevated eosinophil levels after IVIG therapy. Therefore, atopic diseases may develop in EV patients later in childhood, and further studies are warranted to elucidate this issue.

Kuo et al. [9, 11] reported that IL-4, IL-5, and eosinophil levels are increased in KD patients. This suggests that KD tends to elicit a Th2 immune response and may be related to atopic disease development in late childhood. Levels of both Th1- and Th2-related cytokines are reported to be increased during the acute stage of KD including tumor necrosis factor-alpha [5], IL-6, IL-8 [19], IL-4 [2, 6, 12], IL-5, eotaxin, and IL-10 [6]. In our study, the EV patients also had an increased eosinophil level after IVIG therapy. However, neither the IL-5 nor the IL-4 level increased before or after IVIG treatment in a previous report [22]. Thus, the Th1 cytokines levels were increased in both KD and EV patients, whereas the levels of Th2 cytokines were increased only in the KD patients.

In our study, the platelet count increased significantly in the patients with KD but not in the EV patients after IVIG treatment. During progression of the disease, thrombocytosis usually is detected in KD patients [21]. This can exert a pathogenetic influence on the cardiovascular complications that occur in KD, including CAL formation [20]. Wang et al. [23, 24] reported that the CD40 ligand (CD40L) is expressed on CD4 T-cells and platelets in KD patients. In certain types of vasculitis, CD40L has been implicated, and the CD40L expression on CD4 T-cells and platelets but not on CD8 T-cells is significantly correlated with the occurrence of coronary artery dilation [23, 24]. Thrombocytosis after IVIG is found only in patients with KD but not in EV patients, indicating that thrombocytosis is not related to IVIG treatment or the possible role that platelets play in cardiovascular complications of KD.

After IVIG treatment, the KD patients had lower Hb and segment levels but higher platelet, lymphocyte, and eosinophil levels than the EV patients (all $p < 0.05$). The KD patients had a more significant increase in eosinophil levels than the EV patients, which may have been related to a Th2 immune response due to the IVIG treatment or the inflammatory vasculitis itself [12]. The KD patients received almost twice the dosage of IVIG as the EV patients during the acute phase, which also may have contributed to the increase in eosinophil level after IVIG treatment in a dose-dependent effect.

Conclusion

The study results provide evidence that post-IVIG eosinophilia may be related to IVIG therapy. The higher eosinophil count in patients with KD before and after IVIG therapy than in patients with EV may be due to the inflammatory mechanism of KD. The KD patients had increased platelets after IVIG, but this was not found in the EV patients, suggesting that platelets are involved in the inflammatory response to KD.

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Conflict of interest The authors have declared that no competing interests exist.

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