Clinical and Experimental Medicine (2019) 19:87–92
https://doi.org/10.1007/s10238-018-0513-6

ORIGINAL ARTICLE

Association between IL-35 and coronary arterial lesions in children with Kawasaki disease

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Received: 3 March 2018 / Accepted: 18 June 2018 / Published online: 27 July 2018

Abstract

Kawasaki disease (KD) arises due to the acute inflammation and immune system dysfunction. This study investigated the relationship between the serum level of IL-35 and coronary artery lesions (CALs) in patients with KD. We obtained blood samples from 90 children with KD before intravenous immunoglobulin therapy. Levels of IL-35, IL-6, IL-17A, IL-10, MCP-1 and VEGF were measured in 190 cases, including 4 groups: KD with coronary arterial lesions ($n=46$), KD without coronary arteries lesions ($n=44$), febrile control group (FC, $n=40$) and the normal control group (NC, $n=60$). White blood cell counts (WBC), red blood cell counts (RBC), hemoglobin, platelet, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin were tested in all subjects. Levels of IL-35, RBC and hemoglobin significantly decreased, and IL-6, IL-17A, IL-10, MCP-1 and VEGF were significantly elevated in the KD group compared with febrile and control groups. IL-35 serum level even decreased, and ESR, IL-6, MCP-1 and VEGF increased in the KD patients with CALs. Serum levels of IL-35 in KD patients were negatively associated with WBC, CRP, IL-6, IL-17A, IL-10, MCP-1 and VEGF in children with KD. IL-35 may have the effect on inhibiting inflammatory process in KD and further preventing KD patients from coronary artery lesion.

Keywords Kawasaki disease (KD) · Interleukin-35 (IL-35) · Interleukin-17A (IL-17A) · Interleukin-10 (IL-10) · Coronary arterial lesion

Introduction

Kawasaki disease (KD) is an acute febrile disease with coronary and other systemic vasculitis predominantly in infants and children [1]. Its most critical complication is the occurrence of coronary arteritis lesions (CALs) or aneurysms that may lead to myocardial ischemia, infarction and sudden death [2]. Although the factors causing CALs in KD patients have not been clearly identified, previous studies have suggested that acute inflammation and immune system dysfunction contribute to the pathogenic process of CALs in KD patients [3]. Inflammatory cytokines, such as IL-6, IL-17A, IL-10 and tumor necrosis factor (TNF)-a, are increased in the acute phase of KD [4, 5]. There is also evidence that imbalance of T cell subsets that $CD4^+$ T cells increase and $CD8^+$ T cells decrease in peripheral blood is involved in acute and subacute phase of KD and may causing CALs [6].

IL-35 is the most recently identified member of interleukin-12 (IL-12) family, which is composed of Epstein–Barr virus-induced gene protein 3 (EBI3) and the IL-12 p35 subunit (IL-12A) [7]. IL-35 is produced by $CD4^+$ regulatory T (Treg) cells, activated dendritic cells (DCs), macrophages, endothelial cells and aortic smooth muscle cells [7–9]. Recent evidence demonstrates that IL-35 is an important immunosuppressive/anti-inflammatory cytokine and may have the effect on reducing the progression of inflammatory and autoimmune diseases [10, 11]. The immunosuppressive potential of IL-35 might be partially explained by

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its effect on the expansion of Treg cells and increased production of IL-10. Moreover, IL-35 could suppress Teff cell proliferation in vitro and inhibit differentiation of Th17 cells in vivo [7, 12]. Additionally, the observation showed that the plasma IL-35 level is not only a potential predictor for symptoms' onset of coronary artery disease (CAD) including stable angina pectoris (SAP), unstable angina pectoris (UAP), acute myocardial infarction (AMI), but also plays a critical role in myocardial function of CAD [13]. However, whether IL-35 has the effect on pathogenesis of KD is still unknown. Thus, we examined serum concentration of IL-35 and the correlation with other inflammatory cytokines such as IL-17A, IL-10, IL-6, MCP-1 and VEGF in KD patients to ascertain whether IL-35 is involved in the development of KD.

Materials and method

Subjects' recruitment

All selected patients with KD were from the Children's Hospital of Chongqing Medical University, Chongqing, China. Ninety patients (48 males and 42 females, 2.55 ± 1.72 years old) were involved in the study, all of whom met the criteria proposed by the Japanese Kawasaki Disease Research Committee [14]. Sixty healthy children (32 males and 28 females, 2.19 ± 2.22 years old) were considered as normal control group and 40 (20 males and 20 females, 2.84 ± 1.63 years old) children with fever of pneumonia as febrile control group.

Patients with KD were divided into two groups according to the presence of CAL: KD with CALs ($n = 46$) and KD without CALs ($n = 44$). CALs were defined by an internal diameter of artery > 3.0 mm (< 5 years) or > 4.0 mm (≥ 5 years), or if the internal diameter of a segment was at least 1.5 times that of an adjacent coronary artery according to the examination by echocardiography [15]. Echocardiography was obtained within 2 weeks of the onset or before intravenous immunoglobulin administration. All blood samples were drawn before IVIG therapy in KD patients in the first week of illness. Serum was frozen at − 80 °C until assays were performed.

Measurement of serum levels of IL-35, IL-6, IL-17A, IL-10, MCP-1 and VEGF

Serum concentrations of IL-35 (Abeomics, USA), IL-6, IL-17A, IL-10, MCP-1, VEGF (RayBiotech, USA) were measured using enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions.

Statistical analysis

All values in this study are described as mean ± standard deviation (SD) or number and percent (n, %). Comparisons of frequencies between groups were analyzed using Chi-square test. The statistical significance of concentrations of cytokines was determined by one-way ANOVA unpaired two-tailed t test. Pearson's correlation analysis was used to test for associations between sequential parameters. A two-tailed p value of < 0.05 was considered significant. SPSS version 17 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

General laboratory findings and levels of IL-35, IL-17A, IL-10, IL-6, MCP-1 and VEGF

The clinical characteristics of children patients with Kawasaki disease, febrile infectious disease (FC) and normal children (NC) are summarized in Table 1. There were no statistically significant differences in age or gender among three groups ($p > 0.05$) and a significant decrease in RBC and HB ($p < 0.05$). The levels of WBC, platelet, CRP, ESR and PCT were markedly higher in the KD group than those in NC group but similar to those in FC group. The serum levels of IL-35 were decreased, and IL-6, IL-17A, IL-10, MCP-1 and VEGF were markedly elevated in the KD group compared with FC and NC groups (all $p < 0.05$) (Table 1).

Differences in serum IL-35, IL-6, IL-17A, IL-10, MCP-1 and VEGF between group of KD with CALs and group of KD without CALs

There were no significant differences between group of KD with CALs and group of KD without CALs in age, sex, WBC, platelet, RBC, HB, CRP, PCT, IL-17A and IL-10 ($p > 0.05$). However, the serum level of ESR, IL-6, MCP-1 and VEGF was markedly higher in the group of KD patients with CALs than in the group of patients without CALs ($p < 0.05$). Moreover, the serum level of IL-35 markedly decreased in the KD patients with CALs than the group of patients without CALs ($p < 0.05$) (Table 2).

Table 1 Comparison of laboratory characteristic in patients and control groups

	KD ($n=90$)	FC ($n=40$)	NC ($n=60$)	p value
Age (y)	2.55 ± 1.72	2.84 ± 1.63	2.19 ± 2.22	0.102
Sex (male/female)	39/51	20/20	32/28	0.543
Fever time (day)	6.55 ± 1.97	6.75 ± 4.81[a]	0.00 ± 0.00[b]	< 0.001
WBC (10^3/uL)	15.70 ± 6.02*	9.87 ± 3.88[a]	8.23 ± 2.63[b]	< 0.001
Hemoglobin (g/dL)	10.77 ± 1.16*	11.83 ± 1.23[a]	12.61 ± 0.88[b]	< 0.001
Platelet (10^3/uL)	399.39 ± 162.06*	335.43 ± 107.98	301.32 ± 84.59[b]	< 0.001
RBC (10^6/mm^3)	4.07 ± 0.50*	4.43 ± 0.56[a]	4.80 ± 0.44[b]	< 0.001
PCT	0.43 ± 0.16*	0.34 ± 0.10	0.32 ± 0.06[b]	< 0.001
CRP (mg/dL)	61.47 ± 42.81*	17.48 ± 17.28[a]	8.00 ± 0.00[b]	< 0.001
ESR (mm/h)	74.68 ± 24.84	60.26 ± 36.22[a]	8.65 ± 4.28[b]	< 0.001
IL-35 (pg/ml)	15.07 ± 1.37*	24.96 ± 2.98	28.86 ± 4.92[b]	0.001
IL-6 (pg/ml)	158.49 ± 14.53*	88.69 ± 14.16[a]	17.27 ± 6.12[b]	< 0.001
IL-17A (pg/ml)	22.07 ± 3.02*	4.72 ± 0.82[a]	3.20 ± 2.30[b]	< 0.001
IL-10 (pg/ml)	92.89 ± 15.59*	50.40 ± 16.13[a]	12.93 ± 3.30[b]	0.005
MCP-1 (pg/ml)	175.66 ± 16.82*	119.47 ± 13.09	105.64 ± 5.16[b]	< 0.001
VEGF (pg/ml)	270.01 ± 15.80*	205.83 ± 21.04[a]	106.81 ± 10.98[b]	< 0.001

p value is for comparison among KD, FC and NC

KD Kawasaki disease; *NC* healthy controls; *FC* febrile controls; *y* year; *WBC* white blood cell counts; *RBC* red blood cell counts; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate; *PCT* procalcitonin; *MCP-1* monocyte chemoattractant protein-1; *VEGF* vascular endothelial growth factor

*p value of < 0.05 between KD and FC

[a]p value of < 0.05 between FC and NC

[b]p value of < 0.05 between KD and NC

Table 2 Clinical parameters in two groups of KD patients

	KD with CALs ($n=46$)	KD without CALs ($n=44$)	p value
Age (y)	2.54 ± 1.99	2.94 ± 2.52	0.262
Sex (male/female)	24/22	18/26	0.482
Fever time (day)	6.62 ± 2.37	6.48 ± 1.50	0.742
WBC (10^3/uL)	16.32 ± 5.65	15.09 ± 6.37	0.341
Hemoglobin (g/dL)	10.80 ± 1.23	10.75 ± 1.09	0.848
Platelet (10^3/uL)	401.18 ± 155.25	397.59 ± 170.38	0.918
RBC (10^6/mm^3)	4.05 ± 0.53	4.08 ± 0.47	0.761
PCT	0.45 ± 0.15	0.40 ± 0.16	0.197
CRP (mg/dL)	63.26 ± 38.40	62.03 ± 46.01	0.853
ESR (mm/h)	66.86 ± 21.01	77.23 ± 26.55	0.048*
IL-35 (pg/ml)	11.79 ± 1.42	17.64 ± 2.10	0.033*
IL-6 (pg/ml)	190.65 ± 26.60	133.22 ± 14.07	0.049*
IL-17A (pg/ml)	25.49 ± 5.01	18.65 ± 3.33	0.259
IL-10 (pg/ml)	95.39 ± 22.58	90.50 ± 21.79	0.877
MCP-1 (pg/ml)	196.13 ± 22.18	145.35 ± 10.59	0.041*
VEGF (pg/ml)	299.55 ± 20.70	238.28 ± 19.63	0.034*

KD Kawasaki disease; *CALs* coronary artery lesions; *y* year; *WBC* white blood cell counts; *RBC* red blood cell counts; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate; *PCT* procalcitonin; *MCP-1* monocyte chemoattractant protein-1; *VEGF* vascular endothelial growth factor

*p value of < 0.05

Table 3 Correlation of IL-35 with clinical and laboratory variables and pro-inflammatory cytokines in KD patients

	IL-35	
	r	*p*
WBC (10^3/uL)	− 0.288	0.031*
Hemoglobin (g/dL)	0.081	0.519
Platelet (10^3/uL)	0.083	0.507
RBC (10^6/mm^3)	0.021	0.867
PCT	− 0.090	0.554
CRP (mg/dL)	− 0.283	0.038*
ESR (mm/h)	0.256	0.052
IL-6 (pg/ml)	− 0.402	0.034*
IL-17A (pg/ml)	− 0.325	0.020*
IL-10 (pg/ml)	− 0.293	0.039*
MCP-1 (pg/ml)	− 0.305	0.044*
VEGF (pg/ml)	− 0.324	0.030*

KD Kawasaki disease; *WBC* white blood cell counts; *RBC* red blood cell counts; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate; *PCT* procalcitonin; *MCP-1* monocyte chemoattractant protein-1; *VEGF* vascular endothelial growth factor

*p value of < 0.05

Correlations between cytokine and patient characteristics

WBC, CRP, IL-6, IL-17A, IL-10, MCP-1 and VEGF levels were negatively correlated with IL-35 in patient with KD ($p < 0.05$) (Table 3).

Discussion

IL35, a recently identified member of IL-12 family, is an important anti-inflammatory cytokine. This study was conducted to determine the role of IL-35 on the pathogenesis of Kawasaki disease (KD) and to investigate the association between IL-35 and CALs in KD patients. Our study demonstrated that (1) serum levels of IL-35 decreased and IL-6, IL-17A, IL-10, MCP-1 and VEGF increased in KD patients, compared with groups of the normal and febrile controls, and even more (2) IL-35 decreased and IL-6, MCP-1 and VEGF increased in group of KD patients with CALs compared with the group of KD without CALs. Moreover, (3) IL-35 was negatively associated with WBC, CRP, IL-6, IL-17A, IL-10, MCP-1 and VEGF in KD patients.

IL-35, which is mainly produced by Treg cells, can efficiently suppress the activity of $CD4^+$ effector T cells. Some researches have showed that it is involved in regulating the progression of inflammatory and autoimmune diseases such as experimental colitis [16], collagen-induced autoimmune arthritis [12], autoimmune demyelination in central nervous system [17] and type 2 T helper cell (Th2)-mediated allergic asthma [18]. But there are little data describing the role of IL-35 in acute inflammatory diseases like KD. Our study showed that serum IL-35 levels in patients with KD were lower than those in the healthy controls and febrile controls, indicating that IL-35 may have the effect on inhibiting inflammatory process in the vasculitis in acute phase of KD. Furthermore, serum level of IL-35 decreased in the group of KD patients with CALs, compared with the group of KD patients without CALs, which suggested that IL-35 may have the effect on preventing KD patients from coronary artery lesion.

Many studies have suggested that acute inflammation and immune activation contribute to the pathogenic process of KD because several pro-inflammatory and anti-inflammatory cytokines are elevated during the acute phase of KD [3]. The nature of the T cell response in KD is still unclear. Th17 cells produce the essential cytokine IL-17A, and Tregs produce the IL-35 and IL-10 [5, 7, 19]. Our study showed that the serum levels of IL-10 and IL-17A were increased and IL-35 was decreased in KD patients which is in accordance with the previous research [5, 20]. It is in line with the recent research that Th17/Treg cell is imbalanced in the development of the acute vasculitis syndrome of KD [21].

IL-17A may act as a pro-inflammatory cytokine that regulates tissue inflammation by applying on a series of cell types to induce the expression of other cytokines (such as IL-6, TNF-a and IL-8), chemokines and metalloproteinases [22, 23]. Recently, study has showed that IL-35 can suppress production of IL-17, enhance natural Treg function and suppress $CD4^+CD25^-$ conventional responder T cells(Tres) proliferation in vitro [24]. Another report also discovered that IL-35 could suppress IL-17 and IL-6 production by $CD4^+$ T cells [25]. We obtained similar results in this study, where IL-17 and IL-6 levels were negatively correlated with IL-35 level. IL-10 has an important role in immunoregulation and inflammation which could inhibit the production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α [26]. Some studies reveal that IL-35 can enhance IL-10 production by $CD4^+$ T cells to exert anti-inflammatory function [27]. However, we found that IL-10 level was negatively correlated with IL-35 level in KD. Therefore, we have the speculation that IL-35 may have the effect on suppressing the production of IL-6, IL-17 and IL-10 in the acute phase of KD.

In this study, we found that the level of IL-35 was negatively correlated with levels of WBC, CRP, MCP-1 and VEGF in KD patients. MCP-1, a novel C–C chemokine that attracts and activates the monocytes, has been reported to positively correlate with KD development [28–31]. Research has demonstrated that IL-35 could dose-dependently upregulate MCP-1 released by PBMCs [32]. However, our study showed that IL-35 has negative association with MCP-1 in

KD patients, so it can be speculated that IL-35 may have the role on suppressing the production of MCP-1 and may have the effects of anti-inflammation during the acute phase of KD. Elevated WBC and CRP are regarded as predictors of inflammation, and high level of CRP has been reported to be an independent risk factor for the development of giant aneurysms in KD [33]. In addition, several investigators have suggested that VEGF, which is a heparin-binding glycoprotein with potent angiogenic activity specific for endothelial cells and influences vascular permeability, can act as a predictive indicator for the occurrence of CAL in acute KD [34–37]. Moreover, IL-35 could suppress the production of VEGF and inhibit angiogenesis through VEGF/Ang2/Tie2 pathway [38, 39]. Our study showed that IL-35 level was negatively associated with WBC, CRP and VEGF. Hence, it can be speculated that IL-35 may have the role on suppressing the production of VEGF and prevent patients with KD from coronary artery lesion through involving in the anti-inflammatory process.

Major shortcomings of this study are the relatively small number of patients recruited and the absence of comparison with KD patients after treatment with IVIG. More pro-inflammatory cytokines such as IL-1β, TNF-a, INF-γ and TGF-β could not be measured in the same time.

In conclusion, this is the first study to demonstrate that serum IL-35 level decreased in the KD patients, especially in the patients with CALs. Moreover, the levels of IL-17A, IL-10, IL-6, MCP-1 and VEGF were negatively associated with IL-35 in the acute phase of KD. These observations indicated that IL-35 may play an indispensable role in the immunosuppressive/anti-inflammatory response in KD. Further studies are needed to elucidate the exact relationship between IL-35 and IL-17A, IL-10 and other inflammatory cytokines and the mechanism of IL-35 involving in the pathogenesis of KD vasculitis.

Acknowledgements This work was supported by National Natural Science Foundation of China under Grant No. 81500273.

Compliance with ethical standards

Conflict of interest All authors have no actual or potential conflicts of interest with other people or organizations to this work.

Ethical approval The study protocol was approved by the Ethics Committee of Children's Hospital of Chongqing Medicine University, and written informed consent forms were obtained from the parents of all subjects.

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