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ORIGINAL ARTICLE

Relationship between IL-27 and coronary arterial lesions in children with Kawasaki disease

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Abstract Kawasaki disease (KD) arises due to the disorder of the inflammation response and faulty immune regulation. Interleukin-27 (IL-27) is a novel cytokine with both pro-inflammatory and anti-inflammatory effects. This study investigated the relationship between serum levels of IL-27, Interleukin-17A (IL-17A), Interleukin-10 (IL-10), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and coronary artery lesions (CALs) in patients with KD. We obtained blood samples from 81 children with KD before intravenous immunoglobulin (IVIG) therapy. Levels of IL-27, IL-17A, IL-10, IL-6, IL-1β and TNF-α were measured in 251 cases, including 4 groups: the normal control group, NC ($n = 90$), febrile control, FC ($n = 80$), KD without coronary arteries ($n = 41$) and KD with coronary arterial lesions ($n = 40$). White blood cells counts (WBC), red blood cells counts (RBC), hemoglobin, C-reactive protein (CRP), erythrocyte sedimentation rate and procalcitonin (PCT) were tested in all subjects. Levels of IL-27, IL-10, IL-17A, IL-6, IL-1β and TNF-α were significantly elevated, and RBC and hemoglobin significantly decreased in the group of KD group compared with febrile and control groups. IL-27, IL-6, IL-1β and TNF-α serum levels are even higher in KD children with CALs. There was positive relationship between serum levels of IL-27 and WBC, CRP, PCT, IL-10, IL-17A, IL-6 and TNF-α in children with KD. The up-regulation of IL-27 may be closely linked to up-regulation of systemic pro-inflammatory markers in acute KD. Morover, IL-27 may be involved in the development of CALs in acute KD.

Keywords Kawasaki disease (KD) · Interleukin-27 (IL-27) · Interleukin-17A (IL-17A) · Interleukin-10 (IL-10) · Coronary arterial lesion

Introduction

Kawasaki disease (KD) mainly occurs in infants and young children. KD is characterized by the development of acute vasculitis and is the leading cause of acquired heart disease in the pediatric age group in developed countries [1]. Coronary arterial lesions (CALs) are critical complication of KD, leading to myocardial ischemia, infarction and sudden death [2]. The exact series of events in pathogenesis of KD remains unknown; however, there is a growing body of evidence suggests that the development of KD may be an autoimmune-like process [3]. Our laboratory has identified inflammatory cytokines (TNF-a, IL-6 and IL-10) that are thought to play an important role in the development and progression of KD [4]. There is also evidence that disturbed immunological function leading to immunoglobulin-resistant KD may be triggered by an infectious agent in concert with an imbalance of Th17/T cells [5].

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Interleukin-27 (IL-27) is a novel member of the IL-6/IL-12 family [6], which exerts pleiotropic suppressive effects on naive and effector T cell populations during infection and inflammation. IL-27 is expressed by antigen-presenting cells (APCs), monocytes, endothelial cells and dendritic cells [7]. Recent evidence has demonstrated that IL-27 has both pro- and anti-inflammatory effects. Additionally, IL-27 regulates angiogenesis, hematopoiesis and osteoclastogenesis [8–10]. The observations that IL-27 has a profound effect on T cell activation and the production of IL-17A, and IL-10, strongly suggest that IL-27 may serve as a novel diagnostic biomarker for predicting bacterial infection in critically ill patients [11, 12]. However, whether IL-27 modulates the inflammation observed in KD patients is still unknown. Thus, we examined serum concentrations of IL-27, IL-17A, IL-10, IL-6, IL-1β and TNF-α in KD patients to ascertain whether these cytokines are involved in the development of KD.

Materials and methods

Subject recruitment

Patient diagnosis was in strict accordance with the criteria proposed by the Japanese Kawasaki Disease Research Committee [13]. Eighty-one patients (48 males and 33 females, 2.26 ± 1.68 years old) with KD were enrolled from the Children's Hospital of Chongqing Medical University, Chongqing, P.R. China. As controls, 80 children with an acute febrile infectious disease and 90 healthy children were selected.

Echocardiography was obtained within 2 weeks of the onset or before intravenous immunoglobulin administration. Patients with KD were divided into 2 groups according to the presence of CAL: patients with CAL and patients without CALs. CAL was defined by an internal diameter of artery >3.0 mm (<5 years); >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 [14].

All blood samples were drawn before IVIG therapy in the KD patient group. Most of blood samples were collected in the first week of illness. Serum was frozen at −80 °C until assays were performed.

Measurement of serum levels of IL-27, IL-17A, IL-10, IL-6, IL-1β, TNF-α

Serum concentrations of IL-27, IL-17A, IL-10, IL-6, IL-1 β and TNF-α were measured using enzyme-linked immunosorbent assay (ELISA) kit (RayBiotech, USA), according to the manufacturer's instructions. The intra- and inter-assay coefficients of variation for IL-27, IL-10, IL-6, IL-1β and TNF-α were: <10% and <12%. The intra- and inter-assay coefficients of variation for IL-17A were: <7.1 and <9.1%.

Statistical analysis

Statistical analysis was performed using SPSS version 17 software (SPSS Inc., Chicago, IL, USA). We presented the data as mean ± standard deviation (SD) or as median (25th–75th percentile) for all values. One-way analysis of variance (ANOVA) or Kruskal–Wallis ANOVA and Mann–Whitney U tests were used to compare concentrations of cytokines. A Spearman's test was used to measure associations between sequential parameters. A p value of <0.05 was considered to be statistically significant.

Results

General laboratory findings and levels of IL-27, IL-17A, IL-10, IL-6, IL-1β, TNF-α

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 the three groups. There was a statistically significant decrease in RBC (NC: 4.6 ± 0.4, FC: 4.3 ± 0.4, KD: 4.0 ± 0.4 10^6/mm^3) and HB (NC: 123.3 ± 9.5, FC: 113.3 ± 13.5, KD: 106.3 ± 11.0 g/dL) in the KD group. The levels of WBC (NC: 8.7 ± 1.9, FC: 14.2 ± 6.6, KD: 16.5 ± 7.0 10^3/uL), platelet (NC: 359.8 ± 144.7, FC: 376.7 ± 147.1, KD: 393.0 ± 164.3 10^3/uL), CRP (NC: 8.1 ± 0.4, FC: 38.8 ± 30.7, KD: 51.7 ± 36.9 mg/dL), ESR (NC: 4.8 ± 2.4, FC: 65.8 ± 34.3, KD: 76.7 ± 27.2 mm/h) and PCT [NC: 0.2 (0.0–0.2), FC: 1.6 (1.0–2.0), KD: 2.6 (0.1–1.6)] (all p<0.05) were markedly higher in the KD group than that of in NC group but similar to that of in FC group. The serum levels of IL-27 (NC: 335.3 (237.7–520.9), FC: 451.0 (299.6–554.5), KD: 1433.0 (337.7–1318.5) pg/ml), IL-17A (NC: 0.1 (0.0–1.3), FC: 2.1 (0.0–6.1), KD: 30.1 (6.1–52.7) pg/ml), IL-10 (NC: 4.2 (3.2–6.8), FC: 4.2 (3.2–6.8), KD: 13.5 (7.6–26.9) pg/ml), IL-6 (NC: 7.2 ± 2.0, FC: 110.5 ± 21.3, KD: 224.2 ± 32.4 pg/ml), IL-1β (NC: 3.2 ± 0.5, FC: 4.2 ± 1.2, KD: 9.2 ± 1.2 pg/ml) and TNF-α (NC: 17.3 ± 3.8, FC: 19 ± 9.8, KD: 67 ± 9.0 pg/ml) (all p<0.05) were markedly elevated in the KD group compared to the FC and NC groups (Table 1).

Differences in serum IL-27, IL-17A, IL-10, IL-6, IL-1β, TNF-α between KD with and without CALs

There were no significant differences between group of KD with CALs and group of KD without CALs in age, sex,

Table 1 Comparison of laboratory characteristic in patients and controls groups

	NC ($n = 90$)	FC ($n = 80$)	KD ($n = 81$)	p
Age (y)	3.2 ± 2.4	2.6 ± 2.1	2.3 ± 1.7	0.076
Sex (male/female)	37/53	40/40	48/33	0.298
Hemoglobin (g/dL)	123.3 ± 9.5	113.3 ± 13.5#	106.3 ± 11.0*	<0.001
Platelet (10^3/uL)	359.8 ± 144.7	376.7 ± 147.1	393.0 ± 164.3*	0.008
WBC (10^3/uL)	8.7 ± 1.9	14.2 ± 6.6	16.5 ± 7.0*	<0.001
RBC (10^6/mm^3)	4.6 ± 0.4	4.3 ± 0.4#	4.0 ± 0.4*	<0.001
CRP (mg/dL)	8.1 ± 0.4	38.8 ± 30.7	51.7 ± 36.9*	<0.001
ESR (mm/h)	4.8 ± 2.4	65.8 ± 34.3	76.7 ± 27.2*	<0.001
PCT	0.2 (0.0–0.2)	1.6 (1.0–2.0)	2.6 (0.1–1.6)*	<0.001
IL-27 (pg/ml)	335.3 (237.7–520.9)	451.0 (299.6–554.5)#	1433.0 (337.7–1318.5)*	0.004
IL-10 (pg/ml)	4.2 (3.2–6.8)	9.7 (5.7–16.2)#	13.5 (7.6–26.9)*	<0.001
IL-17A (pg/ml)	0.1 (0.0–1.3)	2.1 (0.0–6.1)#	30.1 (6.1–52.7)*	<0.001
IL-6 (pg/ml)	7.2 ± 2.0	110.5 ± 21.3#	224.2 ± 32.4*	<0.05
IL-1 β (pg/ml)	3.2 ± 0.5	4.2 ± 1.2#	9.2 ± 1.2*	<0.05
TNF-α (pg/ml)	17.3 ± 3.8	19 ± 9.8#	67 ± 9.0*	<0.05

KD Kawasaki disease, *NC* healthy controls, *FC* febrile controls, *y* year, *WBC* white blood cells counts. *RBC* red blood cells counts, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin

* A p value of <0.05 between KD and NC

\# A p value of <0.05 between KD and FC

WBC, platelet, RBC, HB, CRP, ESR, PCT, IL-17A and IL-10. However, the serum level of IL-27, IL-6, IL-1β and TNF-α were markedly higher in the KD patients with CALs than in patients without CALs [2157.25 (419.99–2311.62) vs. 779.5 (296.01–778.08) pg/ml] ($p<0.05$), (234.1 ± 133.1 vs. 110.5 ± 73.7 pg/ml) ($p<0.05$), (33.8 ± 18.7 vs. 3.6 ± 0.6 pg/ml) ($p<0.05$), (56 ± 15.4 vs. 21.6 ± 4.6 pg/ml) ($p<0.05$) (Table 2).

Correlations between cytokine and patient characteristics

WBC, CRP, PCT, IL-10, IL-17A, IL-6 IL-1β and TNF-α levels were positively correlated with IL-27 in patients with KD ($r = 0.185$, $p = 0.037$; $r = 0.291$, $p = 0.000$; $r = 0.400$, $p = 0.000$; $r = 0.454$, $p = 0.000$; $r = 0.618$, $p = 0.000$; $r = 0.263$, $p = 0.044$; $r = -0.130$, $p = 0.401$; $r = 0.372$, $p = 0.013$, respectively) (Table 3).

Discussion

L-27 is a heterodimeric cytokine that plays roles in the immune system and inflammation. We were motivated to study the concentrations of IL-27, IL-17A, IL-10, IL-6, IL-1β and TNF-α in children with KD, normal and febrile controls to assess its role in the pathogenesis of KD. Our study demonstrated that (1) levels of IL-27, IL-17A, IL-10, IL-6, IL-1β and TNF-α increased in patients with KD, compared with normal subjects, and (2) serum levels of IL-27 increased in KD patients with CALs, compared with normal subjects and with KD without CALs. Moreover, we found (3) WBC, CRP, PCT, IL-10, IL-17A, IL-6 and TNF-α levels were significantly correlated with IL-27 in patients with KD.

Many studies have reported that immune activation may contribute to its pathogenesis [15] due to the observations that several pro-inflammatory and anti-inflammatory cytokines are elevated during the acute phase of KD. In our previous study we demonstrated that resistin acted as an inflammatory cytokines and levels were significantly higher in patients with KD [16]. There is an ongoing debate on the nature of the T-cell response in development of KD, including the role of regulatory T cells (Tregs) and a subset of T cells known as Th17 cells. Tregs and Th17 cells produce the essential cytokine, and IL-10 and Th17 cells produce the essential cytokine IL-17A. There is a growing body of evidence that the levels of IL-10 and IL-17A increase in patients with KD [17, 18]. This data implicate imbalances in Tregs and Th17 cells in the development of the acute vasculitis syndrome of KD. Recently, some researches have demonstrated that intravenous immunoglobulin (IVIG) suppresses differentiation, amplification, and functions of human Th17 cells and in inhibiting the production of IL-17A from Th17 cells [19–22].

IL-27 plays many roles in the cell, and it was first reported in 2002. It is a heterodimeric cytokine composed of the EBV-transformed gene 3 subunit and p28 subunit. The orphan cytokine receptor WSX-1 was discovered to

Table 2 Relation between clinical parameters in KD patients and development of CALs

	KD without CALs ($n = 41$)	KD with CALs ($n = 40$)	p
Age (y)	2.41 ± 1.88	2.14 ± 1.49	0.466
Sex (male/female)	22/19	26/14	0.368
IL-27 (pg/ml)	779.5 (296.01–778.08)	2157.25 (419.99–2311.62)*	<0.05
IL-10 (pg/ml)	22.9 (7.45–21.19)	28.2 (6.87–31.56)	0.708
IL-17A (pg/ml)	39.2 (7.2–55.4)	42.3 (4.19–51.19)	0.415
IL-6 (pg/ml)	110.5 ± 73.7	234.1 ± 133.1*	<0.05
IL-1 β (pg/ml)	3.6 ± 0.6	33.8 ± 18.7*	<0.05
TNF-α (pg/ml)	21.6 ± 4.6	56 ± 15.4*	<0.05
Hemoglobin (g/dL)	106.194 ± 0.489	106.164 ± 0.481	0.991
Platelet (10^3/uL)	387.40 ± 134.09	411.70 ± 176.57	0.478
WBC (10^3/uL)	16.81 ± 6.44	15.64 ± 7.51	0.445
RBC (10^6/mm^3)	4.04 ± 0.37	4.05 ± 0.48	0.845
CRP (mg/dL)	54.90 ± 46.57	54.93 ± 39.60	0.998
ESR (mm/h)	81.95 ± 27.94	71.33 ± 25.39	0.079
PCT	0.6 (0.1–1.4)	1.3 (0.3–2.6)	0.138

KD Kawasaki disease, *y* year, *WBC* white blood cells counts, *RBC* red blood cells counts, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin. *p* value is for comparison between patients without CAL and those with CAL

* A *p* value of <0.05 between KD with CALs and KD without CALs

Table 3 Correlation of IL-27 with clinical and laboratory variables and pro-inflammatory cytokines in all KD patients

	IL-27			IL-27	
	r	*p*		*r*	*p*
Hemoglobin (g/L)	−0.085	0.340	PCT	0.400	0.000*
Platelet (10^3/uL)	−0.137	0.053	IL-10 (pg/ml)	0.454	0.000*
WBC (10^3/uL)	0.185	0.037*	IL-17A (pg/ml)	0.618	0.000*
RBC (10^6/mm^3)	−0.114	0.203	IL-6 (pg/ml)	0.263	0.044*
CRP (mg/dL)	0.291	0.000*	IL-1 β (pg/ml)	−0.130	0.401
ESR (mm/h)	−0.075	0.428	TNF-α (pg/ml)	0.372	0.013*

KD Kawasaki disease, *WBC* white blood cells counts, *RBC* red blood cells counts, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin

* A *p* value of <0.05

bind to IL-27 and was required for the effect of IL-27. Subsequent work revealed that the second subunit of the IL-27 receptor complex was gp130 [23]. IL-27 is predominantly synthesized by activated antigen-presenting cells including monocytes, endothelial cells and dendritic cells. IL-27 has been observed to be a player in a variety of inflammatory and infectious illness such as septic peritonitis, collagen-induced arthritis and has recently been evaluated as a novel diagnostic biomarker for bacterial infections [24, 25]. Recently, studies have shown that circulating levels of IL-27 are increased in patients with ischemic heart disease, IL-27 also improved cardiac contraction and coronary perfusion [26]. IL-27 can also enhance antitumor immunity by inhibiting regulatory T cell (Treg) differentiation and angiogenesis. IL-27's role in invasion in some immunological disease such as asthma and rheumatoid arthritis has been previously described [27, 28].

Recently, IL-27 was shown to promote IL-10 secretion by human $CD4^+$T cells in vitro. IL-27 suppresses the production of IL-17A from $CD4^+$T cells primarily through a STAT1-dependent mechanism, but research has also demonstrated an effect on STAT3-dependent production of IL-17A by $CD4^+$T cells [29, 30]. At the same time, there is a Th17/Treg cell imbalance in the patients with KD [31]. However, there is little data describing the role of IL-27 in acute inflammatory diseases like KD. This gap in our knowledge prompted us to examine the serum concentrations of IL-27 in children with KD and assess its association with IL-10 and IL-17A in the pathogenesis of KD.

In this study, we showed that the serum levels of IL-10 and IL-17A were increased in KD patients, which is in

accordance with previous research [31, 32]. IL-10 is a potent cytokine that exerts pleiotropic effects on immunoregulation and inflammation [33]. Another report provided support for the role of IL-27 in the regulation of IL-10 production by $CD4^+$cells. These authors also discovered that IL-27 could induce IL-10 production in Th1, Th2 and Th17 cells by acting on the transcription factors STAT1 and STAT3 [34]. In our study, we found that there was a robust positive correlation between the levels of IL-27 and IL-10. Therefore, we hypothesize that IL-27 may induce the production of IL-10 in the acute phase of KD, but further work is required to validate this hypothesis.

IL-17A is a cytokine produced by $CD4^+$T cells. When IL-17A is produced by Th17 cells the cytokine has pro-inflammatory properties that regulate tissue inflammation by acting on a broad range of cell types to induce the expression of other cytokines (such as IL-6, TNF-a and IL-8), chemokines (such as cxcl1, cxcl10) and metalloproteinases [35, 36]. Overexpression of IL-17 has been linked to autoimmune diseases such as rheumatic arthritis and systemic lupus erythematosis [37]. Thus, we know that IL-17 may also act as a pro-inflammatory cytokine. Our study showed that serum levels of IL-17 A were positively correlated to IL-27 levels. This indicates that IL-27 may be associated with the production of IL-17A during the acute phase of KD. Nevertheless, in another autoimmune disease, progressive multiple sclerosis, plasma IL-27 levels were negatively correlated to the percentage of circulating Th17 cells and the concentration of plasma IL-17A [38]. Therefore, further studies are required to explore and clarify the relationship between IL-27 and Th17.

The increased immune response in KD affects multiple organ systems and is particularly centered in the cardiovascular system. These cardiovascular cells also release a variety of cytokines that promote inflammatory vascular injury. Is the IL-27-dependent activation of IL-10 and IL-17A via STAT1 and STAT3 a mechanism in the development of KD? Further experiments will be required to answer this intriguing question.

Previous studies have reported that CRP and PCT are associated with KD [39]. However, few studies have demonstrated a relationship between CRP, PCT and IL-27. In our study we found a positive relationship between IL-27 serum levels and CRP and PCT. These results suggest that IL-27 may be involved in inflammation during the acute phase of KD.

Finally, in this study we confirmed observations from our previous study that showed that the levels of RBC and hemoglobin were decreased in KD [16]. Another laboratory demonstrated that systemic oxidative stress together with premature aging of RBCs could play a critical role in the cardiovascular complications associated with KD [40, 41]. We are very interested in whether or not decreased levels of RBC and hemoglobin are linked to oxidative stress in KD.

Caroline Galeotti et al have shown that IVIG infusion and aspirin are the standard treatment of acute KD. However, 10–20% of patients show resistance to IVIG therapy and present higher risk of coronary vasculitis. The relative roles of second IVIG infusion, corticosteroids, calcineurin inhibitors, IL-1 antagonists and anti-TNF-α agents remain uncertain [42]. Therefore, alternative therapies are expected to provide more options for the management of resistant patients. Both coronary artery bypass surgery and percutaneous intervention have been used to treat Kawasaki disease patients who develop myocardial ischemia as a consequence of coronary artery aneurysms and stenosis [43].

Galeotti [44] also demonstrated that a number of biomarkers in Kawasaki disease have shown potential for predicting response to IVIG. This may serve to guide our future studies in this area. The potential limitations of our study should be noted. As serum levels of IL-27, IL-10 and IL-17A are regulated by many cytokines, chemokines and cells, therefore, more chemokines should be further examined such as monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF). A limitation of the present study was that the sample size of the present study was relatively small. Larger studies and the long-term management are required to confirm our observations.

In conclusion, this is the first study to show significant elevation of serum IL-27 in the KD patients with CALs. Morover, the levels of IL-10, IL-17A, IL-6 and TNF-α were linked to IL-27 serum levels in the acute phase of KD, providing further evidence about the inflammatory role of IL-27 in KD. These observations indicate that IL-27 may play an indispensable role in the immune and inflammation response in KD. Further studies are needed to elucidate the exact relationship between IL-27 and IL-17A, IL-10 and other inflammatory cytokines and the pathogenesis of KD vasculitis.

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Compliance with ethical standards

Conflict of interest All authors have no actual or potential conflicts of interest with other people or organizations with 3 years of initiating the work presented here.

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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