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Decreased levels of inflammatory cytokines in immunoglobulin-resistant Kawasaki disease after plasma exchange

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ABSTRACT

The pathogenesis of coronary artery aneurysm (CAA) formation in Kawasaki disease (KD) remains unknown. However, inflammatory cytokines are thought to play an important role in KD. Patients with intravenous immunoglobulin (IVIG)-resistant KD are more likely to develop CAA. For such refractory patients, steroids and emerging infliximab (IFX) are used; however, further verification is required for their efficacy and safety. Plasma exchange (PE), which removes various inflammatory cytokines, has been used in Japan for over 15 years to prevent CAA in IVIG-resistant KD patients. The sequential change in inflammatory cytokines during the time course of PE has yet to be investigated. In this study, we measured plasma levels of 13 cytokines in nine children with IVIG-resistant KD before the start of PE (day 0: D0), as well as at 1 or 2 days (D1/2), and 4 or 5 days (D4/5) after starting PE. The median age of onset was 8 months (range: 3–53 months). Before PE, patients were treated with IVIG (median dose: 4 g/kg, range: 3–4 g/kg). The median starting period of PE was 8 days after the onset of fever (range: 6–21 days), while its duration was 3 days (range: 2–5 days). Among the 13 cytokines, interleukin-6, tumor necrosis factor-α, tumor necrosis factor receptor I (TNFR1), TNFR2, granulocyte colony-stimulating factor, and IL-17 were significantly lower at D4/5 compared with D0 and/or D1/2, reflecting the potential central efficacy of PE. While three patients developed moderate CAA, their condition regressed within 1 year. The removal of inflammatory cytokines could be the central efficacy of PE against refractory KD.

1. Introduction

Kawasaki disease (KD) is one of the most common forms of vasculitis in children. The annual incidence of KD in Japan increased by 17% from 2005 to 2008. In recent years, nearly 12,000 new cases have been reported each year [1].

Coronary artery aneurysm (CAA) is a critical complication of KD, and develops during the acute phase of the disease. CAA is associated with high morbidity and mortality because of myocardial ischemia, infarction, and sudden death [2]. The use of intravenous immune globulin (IVIG) in combination with aspirin has been proven to be effective in reducing the risk of CAA formation. However, in the absence of IVIG treatment, approximately 20% of KD patients develop CAA [3]. Unfortunately, 10–20% of KD patients show resistance to IVIG and are at higher risk of developing CAA [4,5]. For IVIG-resistant patients, corticosteroids [6], infliximab (IFX) [7], cyclosporine [8], and plasma exchange (PE) [9] are used as alternative therapies. Although corticosteroids have been used for many years, their efficacy, especially in the later days of illness after onset, is still controversial [10,11]. IFX has emerged as a promising therapeutic option in recent years, but its efficacy and safety have yet to be verified.

To date, the pathogenesis of KD is still not been fully elucidated. Activation of innate and adaptive immune systems is thought to be a central feature of KD. There have been many reports on elevation of plasma levels of multiple inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, IL-8, and interferon (IFN)-γ, during the acute phase of KD. TNF-α was found to play a major role in the development of CAA in a mouse model of KD [12–19]. Because PE can remove excessive inflammatory cytokines in the circulation [20], its use in IVIG-resistant KD

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patients is increasing, particularly in Japan [9,21–23]. Despite this situation, few studies have determined the exact plasma cytokine levels during PE [24]. Therefore, we investigated the serial changes in plasma cytokine levels during and after PE, and evaluated the efficacy of PE in association with their levels.

2. Material and methods

2.1. Patients

Nine patients in this study who fulfilled the following two criteria were hospitalized in National Center for Child Health and Development between October 2009 and December 2010: undergoing IVIG more than twice (total IVIG > 3 g/kg), and having continued fever with/without other symptoms of KD 24 h after the last IVIG treatment.

2.2. Measurement of cytokines

Blood samples were collected before (day 0; D0), 1 or 2 days (D1/2), and 4 or 5 days (D4/5) after the initiation of PE. The Milliplex® MAP Immunoassay kit (Merck Millipore, Darmstadt, Germany) was used to measure plasma levels of the following 11 cytokines: IL-6, IL-8, IL-17, IL-10, I-12p70, TNF-α, IFN-γ, monocyte chemoattractant protein-1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), soluble IL-2 receptor (sIL-2R), and vascular endothelial cell growth factor (VEGF). Levels of soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2 were measured by the Cytometric Bead Array System (BD Biosciences, San Jose, CA, USA).

2.3. PE

All of the patients who underwent PE were admitted to a pediatric intensive care unit. Because most of the patients were younger than 1 year old, they were sedated and mechanically ventilated during the procedure for safety. The replacement fluid used was 5% albumin and the exchange volume per day was calculated as 1.5–2 times the total body plasma volume. PE was carried out until fever was resolved (<37.5 °C). After the last PE, most of the patients were administered IVIG to supplement the removed IgG.

2.4. Classification of CAA

We divided CAA into three categories according to severity: (1) dilatation, internal luminal diameter less than 4 mm; (2) moderate CAA, internal luminal diameter between 4 and 8 mm; and (3) giant aneurysms, internal luminal diameter greater than 8 mm. We defined transient dilatation as the diameter of a dilated coronary artery returning to the normal range within 30 days after the onset of fever.

2.5. Statistical analysis

Plasma levels of cytokines and C-reactive protein (CRP), and the white blood cell (WBC) count were statistically analyzed by two-way ANOVA and Steel–Dwass analysis using JMP software (SAS institute, Cary, NC, USA). Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Characteristics of the patients and treatment before PE

The nine patients included in this study included five boys and four girls. Table 1 shows the major symptoms at diagnosis of KD and just before PE, WBC count, and CRP levels just before IVIG and prior to PE. The type of treatment received before PE is shown in Table 2. At the start of PE, all of the patients had persistent fever with a high WBC count and CRP levels, despite IVIG treatment. One patient was treated with IFX, but this was proven as ineffective. Two patients in this study did not fulfill the diagnostic criteria of KD and were considered to have incomplete KD (patients 7 and 8). Incomplete KD was defined as having only four out of the six principal symptoms (in the absence of CAA) outlined in the Japanese diagnostic guidelines, or having fewer than four principal symptoms, regardless of whether the patient had CAA.

3.2. PE and prognosis of CAA

The median time of the first session of PE was 8 days from the onset of fever (range: 6–21 days). The median duration of PE was 3 days (range: 2–5 days). The day of initiation of PE, duration of treatment, the type of treatment after PE, and the clinical course of the patients are shown in Table 3. Before PE, seven patients had no CAA, while one had mild coronary artery dilatation, and another had moderate CAA. Among the seven patients who had no CAA before PE, two developed moderate CAA later; one (patient 9) of these patients required additional therapies (IFX and additional IVIG) because of recurrence of fever (Table 3). Among the two patients who had CAA (including mild coronary artery dilatation) before PE, no further deterioration of coronary lesions was observed in either patient after PE. Moderate CAA was present in three patients 30 days after the onset of KD, but regressed completely 1 year later. There were no severe adverse events during PE.

Table 1
Characteristics of the patients.

Case	Sex	Age at onset (months)	Clinical symptoms as diagnostic criteria (at diagnosis/at initiation of PE)						Laboratory data, just before IVIG		Laboratory data just before PE	
			Fever	Conjunctival injection	Cervical lymph-adenopathy	Changes in the lips and oral cavity	Changes in the extremities	Poly-morphous exanthema	WBC (/μL)	CRP (mg/d L)	WBC (/μL)	CRP (mg/dL)
1	M	53	+/+	+/+	+/−	+/+	+/−	−/−	15,500	15.0	24,200	18.9
2	F	39	+/+	−/+	+/−	+/+	+/−	−/−	13,730	8.9	15,800	5.7
3	F	12	+/+	+/−	+/+	+/−	+/−	+/−	8200	7.3	18,080	16.4
4	M	9	+/+	−/−	+/+	+/+	+/+	+/−	7500	11.5	10,280	12.9
5	F	6	+/+	+/+	+/−	+/+	+/+	+/+	7700	8.3	19,310	16.3
6	M	3	+/+	+/+	−/+	+/+	+/−	+/−	12,500	5.6	17,350	8.9
7[a]	M	3	+/+	+/+	−/−	−/+	+/−	−/−	9900	10.5	16,000	7.0
8[a]	M	4	+/+	−/−	+/−	−/−	+/−	+/+	4760	15.2	14,580	8.0
9	F	8	+/+	+/+	+/+	+/+	+/+	+/+	18,200	2.0	21,590	6.0

+: positive clinical symptom, −: negative clinical symptom.
[a] Incomplete KD, PE: plasma exchange, IVIG; intravenous immunoglobulin, WBC: white blood cell count, CRP: C-reactive protein.