Outcomes of Kawasaki Disease in Families

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ABSTRACT

An epidemiological study showed that a positive family history of Kawasaki disease (KD) was a risk factor for intravenous immunoglobulin (IVIG) therapy resistance, coronary artery lesions (CALs), and KD recurrence. However, real-world outcomes of KD patients with a family history remain unclear. The objective of this study was to elucidate the outcomes of KD patients with a family history in the era of 2 g/kg IVIG therapy. This retrospective study included data from 201 KD patients who underwent acute-phase treatment from January 2009 to June 2020, with 184 (91.5%) receiving 2 g/kg IVIG therapy. The patients were divided into 13 (family group) with and 188 (nonfamily group) without a family history of KD. The rates of IVIG resistance (8.3% vs. 22.1%, $P = 0.315$), rescue therapy (8.3% vs. 12.8%, $P = 1.000$), CALs (0.0% vs. 2.7%, $P = 1.000$), and KD recurrence (0.0% vs. 3.2%, $P = 1.000$) were similar between the family and nonfamily groups.

Keywords: Family, Intravenous immunoglobulin therapy, Kawasaki disease, Outcomes.

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I. INTRODUCTION

Kawasaki disease (KD) is a pediatric systemic vasculitis of unknown etiology for which a genetic influence is suspected [1]. One study showed that the inositol 1, 4, 5-triphosphate 3-kinase C gene is associated significantly with KD susceptibility and an increased risk of coronary artery lesions (CALs) [1]. Several evidences suggest the importance of genetic factors in disease susceptibility and outcome [1]. The incidence of KD is 10 to 20 times higher in Japan than in Western countries [2]. Compared with the general populations, the risk of KD in siblings of affected children is 10 times higher and the incidence in children born to parents with a history of KD is twice as high [3], [4]. Familial aggregation of the disease also has been observed [5].

An epidemiological study showed that a positive family history of KD was a risk factor for intravenous immunoglobulin (IVIG) therapy resistance, CAL development, and KD recurrence [6]. However, real-world outcomes of KD patients with a family history remain unclear. The objective of this study was to elucidate the outcomes of KD patients with a positive family history in the era of 2 g/kg IVIG therapy.

II. PARTICIPANTS AND METHODS

Our institutional ethics committee approved the study protocol and waived the requirement of patient consent due to the retrospective nature of the study.

This retrospective study included data from 215 patients who underwent acute-phase treatment for KD between January 2009 and June 2020 (Fig. 1). KD was diagnosed based on the criteria (Japanese, fifth edition) mentioned in

the diagnostic guidelines for KD until August 2019 and on the revised criteria (Japanese, sixth edition) from September 2019 [7], [8].

Patients with the first episode of KD were included. A total of 14 patients with complications before initial therapy or with follow-up periods of < 2 months were excluded (Fig. 1). Those excluded patients had no family history of KD.

The remaining patients were divided into two groups: those with (family group, $n=13$) and those without (nonfamily group, $n=188$) a family history of KD (Fig. 1). The outcomes were the rates of IVIG resistance, rescue therapy, CALs, and KD recurrence.

Fig. 1. Study profile.

KD: Kawasaki disease, CAL: coronary artery lesion.

A positive family history of KD was defined as KD in siblings or in children born to parents with a history of KD. IVIG resistance was defined as a fever that persisted or recurred 24 h after initial treatment [9]. KD presentation was defined as relapse when a second episode occurred within 2 months of the first episode after initial defervescence [10], [11]. Defervescence was defined as a body temperature $< 37.5^{\circ}\text{C}$ for at least 24 h, and the defervescence time was the moment when the body temperature reached $< 37.5^{\circ}\text{C}$. Recurrent KD was defined as a secondary presentation of another episode 2 months after an initial episode [10], [11].

A. Initial Therapy

During the study period, an initial single IVIG infusion of 2 g/kg/dose, starting on day 5 of the illness, was given as initial therapy, whenever possible [12]. Patients without inflammation or complications at presentation received acute-phase therapy without IVIG [12]. Between January 2009 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the initial IVIG infusion ended [13]. Aspirin and flurbiprofen were begun at 30 and 3–5 mg/kg/day, respectively, and decreased to 5–10 and 3 mg/kg/day, respectively, once the patient was afebrile [13]. Each treating physician chose aspirin or flurbiprofen after considering the patient's liver function and the risk of Reye syndrome during the influenza season. After December 2017, low-dose aspirin (5 mg/kg/day) was begun on days 8 to 10 of illness after completion of IVIG infusion, including the second course of therapy [12].

B. Rescue Therapy

The decision to use rescue therapies in resistant patients was made 48 to 72 h after completion of the initial IVIG therapy. The decision was made comprehensively according to clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data [12]. Course 2 of therapy comprised rescue IVIG therapy at 2 g/kg/dose, and course 3 was an ulinastatin infusion, the third course of IVIG therapy, or plasma exchange [12].

C. Diagnosis of CAL

CALs were diagnosed using echocardiography based on the Japanese criteria reported by Kobayashi et al [14]. A CAL was diagnosed if any examination showed an internal lumen diameter of ≥ 3 mm in a patient younger than 5 years or a diameter of ≥ 4 mm in a patient older than 5 years if the internal diameter of a segment was at least 1.5 times that of an adjacent segment or if the lumen appeared irregular. A transient CAL was defined as the disappearance of a CAL within 30 days of the illness.

D. Statistical Analysis

Statistical analyses were conducted using Stat Flex Version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Chi-square, Fisher's exact, and Mann-Whitney U tests were used as appropriate, with sample size considerations. $P < 0.05$ was considered statistically significant.

III. RESULTS

The family group included 13 patients (10 siblings and three children born to parents with a history of KD) (Tables

I, II, and III). Of the five sibling pairs, the older sibling presented with KD first in three pairs and four pairs had intervals of KD onset between the first and second sibling of > 1 year (Table I). No patient in the family group had incomplete KD (Tables I and III).

Of the 13 patients in the family group, 12 received 2 g/kg/dose IVIG therapy on day 5 or 6 of illness, and 11 of them (91.7%) responded (Tables II and III). No patient in the family group had CAL at < 1 and 1 month after KD onset (Tables II and III). During a median follow-up of 4 years and 5 months (range: 3 months–6 years and 1 month) after KD onset, no patient in the family group had recurrent KD.

The rates of IVIG resistance (8.3% vs. 22.1%, $P = 0.315$), rescue therapy (8.3% vs. 12.8%, $P = 1.000$), CALs (0.0% vs. 2.7%, $P = 1.000$), and KD recurrence (0.0% vs. 3.2%, $P = 1.000$) were similar between the two groups (Table IV).

TABLE I: BASELINE CHARACTERISTICS OF SIBLING WITH KAWASAKI DISEASE

Pt	Gender	Age	Siblings	Interval	Major signs
Siblings 1					
First onset pt	Male	9 m	Older	6 y and 0 m	5
Siblings 1					
Second onset pt	Female	2 y and 0 m	Younger	6 y and 0 m	6
Siblings 2					
First onset pt	Male	4 y and 9 m	Older	6 y and 3 m	5
Siblings 2					
Second onset pt	Female	2 y and 8 m	Younger	6 y and 3 m	6
Siblings 3					
First onset pt	Male	2 y and 10 m	Younger	7 days	6
Siblings 3					
Second onset pt	Female	4 y and 0 m	Older	7 days	6
Siblings 4					
First onset pt	Female	4 y and 2 m	Younger	1 y and 8 m	6
Siblings 4					
Second onset pt	Female	4 m	Older	1 y and 8 m	5
Siblings 5					
First onset pt	Female	2 y and 6 m	Older	6 y and 5 m	5
Siblings 5					
Second onset pt	Male	4 y and 5 m	Younger	6 y and 5 m	6

Pt: patient, KD: Kawasaki disease, Age: age at KD onset, y: years, m: months, Interval: interval period of KD onset between the first and the second patient, Major signs: number of KD major signs.

TABLE II: TREATMENT AND OUTCOMES OF SIBLINGS WITH KAWASAKI DISEASE

Pt	IVIG (start day of illness)	Aspirin / flurbiprofen	CAL
Siblings 1	Responder	Medium-dose aspirin	None
First onset pt	(5)		
Siblings 1	Responder	Low-dose aspirin	None
Second onset pt	(6)		
Siblings 2	Responder	Medium-dose aspirin	None
First onset pt	(6)		
Siblings 2	Responder	Low-dose aspirin	None
Second onset pt	(5)		
Siblings 3	Responder	Low-dose aspirin	None
First onset pt	(5)		
Siblings 3	Responder	Low-dose aspirin	None
Second onset pt	(5)		
Siblings 4	Responder	Flurbiprofen	None
First onset pt	(5)		
Siblings 4	Responder	Medium-dose aspirin	None
Second onset pt	(5)		
Siblings 5	Responder	Low-dose aspirin	None
First onset pt	(5)		
Siblings 5	Responder	Medium-dose aspirin	None
Second onset pt	(6)		

Pt: patient, IVIG: intravenous immunoglobulin therapy, CAL: coronary artery lesion.

TABLE III: BASELINE CHARACTERISTICS OF PATIENTS WITH PARENTS ASSOCIATED WITH KAWASAKI DISEASE IN CHILDHOOD

Pt number	11	12	13
Gender	Female	Female	Female
Age	2 y and 10 m	3 y and 7 m	2 y and 0 m
Parents with KD	Father	Mother	Mother
Major signs	6	5	5
IVIG (start day of illness)	Non-responder (5)	Responder (6)	Responder (5)
CAL	None	None	None

Pt: patient, KD: Kawasaki disease, Age: age at KD onset, y: years, m: months, Major signs: number of KD major signs, IVIG: intravenous immunoglobulin therapy, CAL: coronary artery lesion.

TABLE IV: COMPARISON OF CLINICAL FINDINGS BETWEEN FAMILY GROUP AND NONFAMILY GROUP

Variables	Family group (n=13)	Non-family group (n=188)	P-value
Male gender	4 (30.8%)	95 (50.5%)	0.168
Age at KD onset (months)	32.0 (20.3-48.5)	26.0 (14.0-45.5)	0.792
Incomplete type	0 (0.0%)	39 (20.7%)	0.077
Low-dose aspirin /	5 (38.5%) /	35 (18.6%) /	0.077
medium-dose aspirin /	7 (53.8%) /	89 (47.3%) /	
flurbiprofen	1 (7.7%)	64 (30.4%)	
IVIG	12 (92.3%)	172 (91.5%)	1.000
Day of illness at initial IVIG therapy	5.0 (5.0-6.0)	5.0 (5.0-6.0)	0.453
Non-responder	1 (8.3%)	38 (22.1%)	0.315
Rescue therapy	1 (8.3%)	22 (12.8%)	1.000
For non-responder	1 (8.3%)	16 (9.3%)	1.000
For relapse	0 (0.0%)	5 (2.9%)	1.000
For responder	0 (0.0%)	1 (0.6%)	1.000
CAL	0 (0.0%)	5 (2.7 %)	1.000
Less than one month after KD onset	0 (0.0%)	5 (2.7 %)	1.000
One month after KD onset	0 (0.0%)	2 (1.1%)	1.000
Recurrence	0 (0.0%)	6 (3.2%)	1.000
Follow-up periods (months)	53 (11.3-62.5)	41.0 (14.0-61.5)	0.853

Data are presents as n (%) or median (interquartile range)/

Incomplete type: major signs of KD ≤ 4 , KD: Kawasaki disease, IVIG: intravenous immunoglobulin therapy, CAL: coronary artery lesion.

IV. DISCUSSION

The main findings of this study were that the rates of IVIG resistance, rescue therapy, CALs, and KD recurrence were similar between the family and nonfamily groups (Table IV). These findings suggested that a positive family history of KD is not a risk factor for IVIG therapy resistance, CAL development, and KD recurrence in the era of 2 g/kg IVIG therapy.

One study using multivariable Cox regression analysis identified a positive family history as independently associated with major cardiac events in patients with dilated cardiomyopathy [15]. However, real-world outcomes of KD patients with a family history remain unclear in the era of 2 g/kg IVIG therapy. One Japanese epidemiological study showed that a positive family history of KD was a risk factor for IVIG therapy resistance, CAL development, and KD recurrence [6]. This was a cross-sectional study using

data from nationwide surveys of KD patients between 1999 and 2002 [6]. Furthermore, one study of KD siblings in North America conducted between 1997 and 2003 demonstrated higher rates of KD recurrence (20.0%), IVIG retreatment (45.5%), and CAL development (20.0%) [5].

The mainstay of current standard therapy in the acute-phase of KD is 2 g/kg IVIG and the evidence regarding CAL suppression of 2 g/kg IVIG therapy has been established [9]. Of the 201 patients, 184 (91.5%) received 2 g/kg IVIG therapy in the present study (Table IV). Conversely, 2 g/kg IVIG was not widespread as acute-phase standard therapy for KD in 1997–2003. This may be a reason for the different outcomes in KD patients with a positive family history between the previous study and the present study.

Addition of medium or high-dose aspirin to 2 g/kg IVIG therapy presently is controversial [16]. A randomized controlled trial on the effectiveness of IVIG monotherapy and IVIG combined with high-dose aspirin in the acute KD stage is ongoing [17]. Studies suggested that aspirin may inhibit CAL prevention and that delayed use of aspirin (DUA) may be beneficial for the suppression of CALs and prevention of coronary artery stenosis in patients with KD [13], [18]–[20]. Furthermore, a recent study showed favorable medium-term outcomes of CALs in KD patients who received 2 g/kg IVIG with DUA [12]. The incidence of KD recurrence is high among those with cardiac sequelae during the initial episode [10]. The low rate of CALs during the first episode may be a factor for the lower rate of KD recurrence [12]. The use of 2 g/kg IVIG therapy with DUA in the present study may be an additional reason for the favorable outcomes in KD patients with a positive family history of KD.

Siblings may have incomplete or atypical KD, which may go unnoticed, and these children may suffer CAL despite normal initial echocardiography [21]–[24]. Incomplete KD or atypical KD may lead to delay in diagnosis and treatment. This is a risk factor for CAL development. Fortunately, no patient in the family group, including siblings, had incomplete KD or atypical KD and received delayed initial IVIG therapy (Tables I, II, and III). The prevalence of CALs in patients receiving IVIG therapy on day 7 of illness was significantly higher than that in patients receiving the therapy before day 7 ($P = 0.024$) [25]. A total of 12 family group patients received initial IVIG therapy between days 5 and 6 of illness (Tables II and III). This may be another reason for the favorable outcomes in our family group patients.

The epidemiological study regarding KD patients from 1999 to 2000 showed that the prevalence of KD recurrence and incidence involving siblings of patients whose parents had a history of the disease were five or six times higher than those of all patients [4]. In the present study, three patients whose parents had a history of KD did not have either KD recurrence or siblings with KD. The mentioned study also showed a high probability of the positive past history of KD among parents with KD children [4]. However, the parents of the KD siblings did not have a history of KD in the present study. Further studies are warranted to elucidate the risk and clinical features regarding KD in families in the era of 2 g/kg IVIG therapy.

A nationwide epidemiological survey of KD in Japan (2015–2016) showed that 661 of 31,595 patients (2.1%) had ≥ 1 sibling affected by KD and 368 (1.2%) had a parent with a history of KD [26]. In the present study of 215 KD patients, the rates of KD siblings and parents with a history of KD were 4.7% and 1.4%, respectively. The higher rate of siblings may be due to bias based on the small sample size of this study.

One study showed that only two (22.2%) of the nine sibling pairs had onset of disease within 1 month of each other, whereas in six pairs, the onset of disease was separated by at least 1 year [5]. This finding was consistent with that in the present study: only one (20.0%) of the five sibling pairs had onset of disease within 1 month of each other, whereas in four pairs, the onset of disease was separated by at least 1 year (Table I). An epidemiological study suggested that genetic mechanism and several infectious agents are involved in KD [26]. The extraordinarily high incidence of the disease and short interval between onsets in twins suggests an increased likelihood of common exposure of twins to an infectious agent and also the possibility of a genetically determined susceptibility factor [3].

Infections are considered to be a trigger for KD, especially in genetically susceptible hosts [27]. KD occurring within a short interval among sibling children is an essential clinical observation supporting this hypothesis [27]. However, of the >201 sibling pairs reviewed, a specific infectious trigger was documented in only five pairs, which included streptococcus, adenovirus, parvovirus, varicella-zoster virus, and measles virus [27]–[29]. In the present study, a specific infectious trigger was not documented in sibling pair number 3 with a 7-day interval (Table I). The siblings are likely to have similar genetic backgrounds and exposure to environmental risk factors [27]. Analysis of tropospheric winds transporting infectious or toxic agents in relation to the occurrence of KD reveals a probable incubation period of 6 to 48 h, thereby reflecting a host response to the antigen or toxin rather than an infection per se [30]. In such circumstances, KD probably would occur simultaneously in siblings [27].

One study showed that the older sibling often presented with KD first and that this probably is a reflection of a greater likelihood of exposure to an infectious trigger [27]. This could be a result of the older sibling becoming infected at school/daycare and passing on the putative infectious agent to the younger sibling at home [27]. Of the five sibling pairs, the older sibling presented with KD first in the three pairs in the present study, whereas a specific infectious trigger was not documented (Table I).

The limitations of this study include the small sample size and the retrospective study design.

In conclusion, the rates of IVIG resistance, rescue therapy, CALs, and KD recurrence were similar between the family and nonfamily groups. These findings suggested that a positive family history of KD is not a risk factor for IVIG therapy resistance, CAL development, and KD recurrence, and that further studies are warranted to elucidate the risk of KD in families in the era of 2 g/kg IVIG therapy.

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