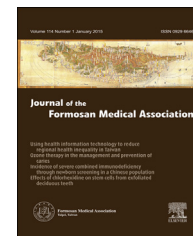Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Transmission of acute infectious illness among cases of Kawasaki disease and their household members

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Background/purpose: Kawasaki disease (KD) is a disease of unknown cause and the causative agent is most likely to be infectious in nature. To investigate the household transmission pattern of infectious illness and etiology, we thus initiated a prospective case and household study.
Methods: We enrolled KD cases and their household members from February 2004 to September 2008. The KD cases and their household members accepted questionnaire-based interviews of the contact history, signs of infection, and symptoms to check whether clusters of infectious illness occurred.
Results: A total of 142 KD cases and 561 household members were enrolled. Among the 142 KD cases, 136 cases (96%) were typical KD, and six (4%) were atypical KD. Of the 561 household members, 17% were siblings, 46% were parents, 18% were grandparents, and the others were cousins or babysitters. Prior to the onset of their KD illness, 66% (94/142) KD cases had contact with ill household members. On the same day of the onset of KD cases' illness, 4% (6/142) KD cases had household members with illness. After KD cases' disease onset, 70% (100/142) KD cases had at least one other family member with illness. Overall, 61% (343/561) of all the household members had acute infectious illness during KD cases' acute stage, and 92% (130/142) of the families had clusters of infectious illness.

Conclusion: A total of 66% KD cases had positive contact with ill household members prior to their disease onset and 92% of families had clusters of infectious illness, so KD is strongly associated with infections.

Introduction

Kawasaki disease (KD) is an acute systemic febrile illness of unknown etiology, predominantly affecting children < 5 years of age. Initially described in 1967 by Tomisaku Kawasaki,[1] it is now the most common cause of acquired heart diseases in children in the developed world, since rheumatic heart disease occurs much less frequently than before. KD is associated with a range of complications, the most important of which is the development of life-threatening coronary artery abnormalities.

There are reported incidence differences in different countries. Asian countries are reported to have higher incidences of KD (30—200/100,000 children < 5 years of age) than Western countries (3.5—10/100,000 children < 5 years of age).[2—10] We reported that KD has seasonal clustering, and usually the peak occurred in the summer, and the annual incidence was 50—70/100,000 children < 5 years of age from 1996 to 2006.[11] The etiology of KD is still controversial and infectious etiology is considered to be one of the predisposing factors. The infectious evidence of KD includes temporal clustering and marked seasonality, geographic clustering, family clustering, high association between KD and infection disease surveillance,[11—13] and age distribution with the highest incidence among 6-month-old to 2-year-old children,[11] who have little maternal antibodies and are most susceptible to infection in general. We hypothesize that infection with certain microorganisms may trigger systemic inflammation, and then small and median sized vasculitis in certain hosts. The important susceptible genes for KD include the immunoglobulin G receptor gene *FCGR2A*, B-lymphoid tyrosine kinase (BLK) region at 8p22-23, the human leukocyte antigen (HLA) region at 6p21.3, and in the CD40 region at 20q13.[14—16] The microorganisms may be transmitted within households and the infected household members may have illness, but only children with certain host genetics develop KD. To confirm the above hypothesis, we did a prospective household and case study for KD to investigate the transmission pattern and the cluster rate of infectious illness among the household members of KD cases.

Patients and methods

KD case enrollment

At the National Taiwan University Hospital in Taipei City and the other collaborative hospitals including Taiwan Adventist Hospital in Taipei City, Far Eastern Memorial Hospital in Taipei County and Min-Sheng Hospital in Tao-Yuan County in Taiwan, we enrolled patients of KD and their household family members from February 2004 to September 2008. The Institutional Review Board of the National Taiwan University Hospital approved this study and informed consents were obtained from all participants or their parents.

The classic diagnosis of KD has been based on the presence of ≥ 5 days of fever and more than four of the five principal clinical features including neck lymphadenopathy, lip fissure and/or strawberry tongue, skin rash, nonpurulent bulbar conjunctivitis, palm/sole erythema and induration followed by desquamation.[17] Patients with fever for ≥ 5 days and less than four principal features can be diagnosed as having KD when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography.[17] The onset of KD cases' illness was defined as the 1st day of fever onset.

After informed consent was obtained from the parents, a questionnaire interview was done to solicit clinical symptoms and preceding contact history with household members with infectious illness or with extra-household ill people. Their clinical laboratory data and coronary arterial lesions were collected.

Two-dimensional echocardiography was performed in all patients during hospitalization, and was repeated at convalescence, 8 weeks after discharge. Coronary arterial abnormality was defined as coronary arterial dilatation/ectasia, aneurysm, increased echogenicity or irregularity, and coronary artery aneurysm. A coronary artery aneurysm was defined as having a lumen diameter (inner border to inner border) of ≥ 3 mm in KD cases < 5 years old and ≥ 4 mm in cases > 5 years old,[14] and giant aneurysm was defined as a lumen diameter of ≥ 8 mm.[18,19]

Enrollment of household members

Household members were defined as people who lived with KD cases. People were defined as household members if they had stayed overnight in the same house with the KD patient for at least 1 night within 10 days prior to or after the onset of his or her symptoms. After informed consent was obtained, household members of KD cases were asked to a questionnaire-based interview including demographic data, and presence of current or recent signs and symptoms of infections 1—10 days prior to, on the same day of, or 1—10 days after the onset of the illness of their household KD case. We took throat swabs for vial isolation from the household members if they had infectious illness when KD patients were admitted to the hospitals in the acute stage. A household cluster of infectious illness was defined as at least one member having infectious illness in one family in addition to the KD case.

Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables, and medians and interquartile ranges for continuous variables. Data were analyzed with the SAS Statistical Package (Version 8.2, SAS Institute, Cary, NC, USA).

Results

Demography and clinical profiles of KD cases

The demography and clinical features of the 142 KD cases are shown in Table 1. Their mean age was 2.1 years, the median age 1.6 years and the male to female ratio was 90 to 52; 136 (96%) were typical KD cases and six (4%) KD cases had fever for $\geq$ 5 days and less than four principal features, but had a coronary arterial aneurysm. In addition to the six typical symptoms (fever, skin rash, bulbar conjunctivitis, red lip/strawberry tongue, neck lymphadenopathy, palm/sole induration with periungual desquamation) of KD, 99 (70%) cases also had cough, 87 (61%) rhinorrhea, and 81 (57%) diarrhea. During the acute stage (2 weeks within the onset), 58 (41%) of KD cases had coronary artery abnormality. At convalescence (2 months after the onset), 23 (16%) still had coronary artery abnormality.

Table 1 Demography and clinical features of 142 Kawasaki disease (KD) cases.

Clinical feature	$n = 142$
Age (y)	
Mean (SD)	2.11 (1.76)
Median (range)	1.6
	(0.16~7.45)
Gender (M/F)	90/52
Principal features	
Fever duration (Day)	
Mean (SD)	7.66 (2.55)
Peak body temperature, mean (SD) (°C)	39.8 (0.6)
Red lip and/or strawberry tongue	136 (96)
Bulbar conjunctivitis	137 (98)
Neck lymphadenopathy	63 (44)
Skin rash	132 (94)
BCG scar	61 (43)
Palm/sole induration followed by desquamation	141 (99)
Palm/sole induration	101 (72)
Desquamation	139 (98)
Other than principal features	
Cough	99 (70)
Rhinorrhea	87 (61)
Diarrhea	81 (57)
Typical KD	136 (96)
Atypical KD*	6 (4)

Data are presented as n (%), unless otherwise indicated.
*Patients with fever for $\geq$ 5 days and less than four principal features plus coronary arterial aneurysm.
BCG = Bacillus Calmette-Guérin; SD = standard deviation.

Household members and positive viral isolation

Among the families of 142 KD cases, we enrolled a total of 561 household members, including 406 adults (72%) and 155 children (28%) as shown in Table 2. They were 95 siblings, 132 mothers, 123 fathers, 65 grandmothers, 38 grandfathers, and 108 others, such as babysitters or cousins. In total, we collected 329 throat swabs for viral isolation from the household members of 135 KD patients, because these household members had an acute infectious illness. Household members of seven KD patients refused to receive throat swabs for viral isolation. The culture results are shown in Table 3. Among the 135 families with throat swab samples, positive viral isolation was found in 8.1% (11/135) families, including enterovirus (4 cases), influenza virus (4 cases), adenovirus (2 cases), and respiratory syncytial virus (RSV; 1 case).

Table 2 Demography and acute infectious illness among 561 household members of 142 Kawasaki disease (KD) patients.

Total household number	561
Adult	72 (406/561)
Children	28 (155/561)
Relationship to KD patient	
Sibling	95
Mother	132
Father	123
Grandmother	65
Grandfather	38
Others	108
Household member having acute infectious illness	61 (343/561)
Sibling with illness	84 (80/95)
Mother with illness	61 (81/132)
Father with illness	53 (65/123)
Grandmother with illness	45 (29/65)
Grandfather with illness	29 (11/38)
Others with illness	71 (77/108)
Cluster in household members	92 (130/142)

Data are presented as n or % (n/N).

Table 3 Viral isolation from household members of 135 Kawasaki disease (KD) patients.

Virus	n (%)
Positive culture rate	11 (8.1)
Enterovirus	4
Influenza virus	4
Adenovirus	2
Respiratory syncytial virus	1

Household cluster

Contact and illness of household members prior to the onset of KD cases' illness

The data of contact history and household cluster are summarized in Fig. 1. From 1 day to 10 day prior to KD cases' illness, 66% (94/142) KD cases had contact with household members with acute infectious illness, including 13% (75/561) of household members with upper respiratory tract infection (URI), 7.1% (40/561) with pharyngotonsillitis, 2.3% (13/561) with acute gastroenteritis (AGE), 0.7% (4/561) with lower respiratory tract infection (LRI), 0.5% (3/561) with fever, 0.4% (2/561) with conjunctivitis, 0.4% (2/561) with hand, foot, and mouth disease (HFMD)/herpangina, and so on.

Illness of household members at and after the onset of KD cases' illness

On the same day of the onset of six KD cases' illness, 10 household members had illness including URI 1% (8/561), pharyngitis/tonsillitis 0.4% (2/561), AGE 0.2% (1/561), and other 0.7% (4/561).

From 1 day to 10 days after the onset of 100 (70%) KD cases' illness, 186 (33%) household members had acute illness including URI (16%, 87/561), pharyngitis/tonsillitis (11%, 62/561), AGE (3.2%, 18/561), fever (1%, 6/561), LRI (0.2%, 1/561), conjunctivitis (0.5%, 3/561), HFMD/herpangina (0.4%, 2/561), and other (7.5%, 42/561).
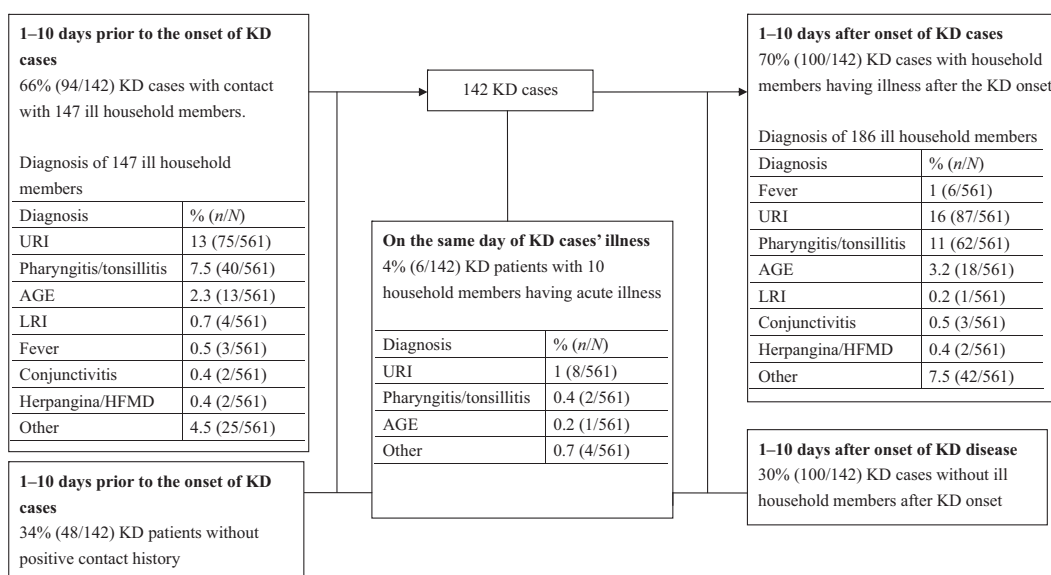
Overall, 92% of KD cases had at least one household member with illness, that is, 92% had a family cluster of acute infectious illness. Of all the 561 household members, 61% (343/561) had acute infectious illness during the acute stage of KD cases' illness, and their siblings had the highest rate (84%) of acute infectious illness (Table 2).

Discussion

KD is a syndrome of undetermined etiology and many studies were done to find the possible infectious, host genetic, or immunological etiologies. However, neither a single pathogen nor a definite gene was found to be the etiology of KD. Our study revealed that obvious infectious illness occurred among the household members of KD cases prior to and after the onset of their KD, and a very high rate of 92% of families had clusters of acute infectious illness. Therefore, our results provide strong evidence that KD was associated with infections in addition to previous researches.

In the viral isolation from KD cases' household members, the positive yield rate was only 3.3%, including enterovirus, influenza virus, adenovirus, and RSV. However, there were no other available data to be compared with. Although a pathogen was isolated from KD patients in another study, there was still no unique virus to be strongly associated with KD.[20,21]

From the clinical features of KD, we found that most of the KD cases had the other symptoms in addition to the six typical symptoms of KD. These included cough (70%), rhinorrhea (61%), and diarrhea (57%). These symptoms may be a result of respiratory or gastrointestinal tract infection. Where and from whom did they get the infection? Because we knew that most (70−90%) of KD cases were < 5 years of age, most of their infections may have come from household members, babysitters, or daycare centers or kindergartens. From the contact history of KD cases, we found that 66% (94/142) of KD cases had positive contact with ill household members, so most of them might get infections from their household members. Subsequently, 70% (100/142) of KD cases might transmit the infections to the other

1–10 days prior to the onset of KD cases
66% (94/142) KD cases with contact with 147 ill household members.

Diagnosis of 147 ill household members

Diagnosis	% (n/N)
URI	13 (75/561)
Pharyngitis/tonsillitis	7.5 (40/561)
AGE	2.3 (13/561)
LRI	0.7 (4/561)
Fever	0.5 (3/561)
Conjunctivitis	0.4 (2/561)
Herpangina/HFMD	0.4 (2/561)
Other	4.5 (25/561)

1–10 days prior to the onset of KD cases
34% (48/142) KD patients without positive contact history

142 KD cases

On the same day of KD cases' illness
4% (6/142) KD patients with 10 household members having acute illness

Diagnosis	% (n/N)
URI	1 (8/561)
Pharyngitis/tonsillitis	0.4 (2/561)
AGE	0.2 (1/561)
Other	0.7 (4/561)

1–10 days after onset of KD cases
70% (100/142) KD cases with household members having illness after the KD onset

Diagnosis of 186 ill household members

Diagnosis	% (n/N)
Fever	1 (6/561)
URI	16 (87/561)
Pharyngitis/tonsillitis	11 (62/561)
AGE	3.2 (18/561)
LRI	0.2 (1/561)
Conjunctivitis	0.5 (3/561)
Herpangina/HFMD	0.4 (2/561)
Other	7.5 (42/561)

1–10 days after onset of KD disease
30% (100/142) KD cases without ill household members after KD onset

AGE = acute gastroenteritis; HFMD = hand, foot, and mouth disease; LRI = lower respiratory tract infection; URI = upper respiratory traction infection.

Figure 1 Contact and transmission of infectious illness within 142 Kawasaki disease (KD) households. AGE = acute gastroenteritis; HFMD = hand, foot, and mouth disease; LRI = lower respiratory tract infection; URI = upper respiratory traction infection.

household members which developed symptoms 1—10 days after the onset of KD cases' illness (Fig. 1).

The clinical diagnosis of ill household members was usually the common cold, however, after transmission to young children with KD, they usually also had URI in the beginning and progressively developed red eye (bulbar conjunctivitis), skin rash, red lip with/without strawberry and palm/sole induration several days later. These phenomena may emphasize the fact that the infectious etiology may be the trigger factors and cause KD in children with special genetic background or environmental characteristics.

To further verify the infectious etiology of KD, thorough investigations on viral, bacterial, mycoplasma, or even fungal pathogens are warranted. A unique unidentified pathogen is a possible cause of KD. The other possibility is that various pathogens may be found to be involved in KD cases and cause medium-sized vasculitis. There are some limitations in this study. For example, no control households of non-KD cases were enrolled for viral isolation.

In conclusion, 66% KD cases had positive contact with ill household members prior to their disease onset and 92% families with KD cases had clusters of infectious illness, so KD is strongly associated with infections.

Acknowledgments

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