

Epidemiologic survey of Kawasaki disease in Inner Mongolia, China, between 2001 and 2013

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Abstract. The epidemiologic features of Kawasaki disease (KD) in the Inner Mongolia Autonomous Region of China has not been previously determined, to the best of our knowledge. Therefore, the aim of the present study was to investigate the epidemiology of KD in Inner Mongolia. Clinical data from 518 patients treated for KD in Inner Mongolia between January 2001 and December 2013 were analyzed. The results indicated that the mean annual incidence rate was 3.55 ± 2.96 per 100,000 children under the age of 5 years between 2001 and 2013. The age at diagnosis ranged between 49 days and 14 years, while the disease occurred more frequently in the spring and summer. In addition, the incidence of coronary artery lesion (CAL) was reported to be 40.2% in the present survey. KD patients in the Han Chinese ethnic group were more likely to be complicated by CAL, whereas patients with incidence of KD in July were less likely to be complicated by CAL. In conclusion, the incidence of KD was observed to be increasing in Inner Mongolia, while the ethnic group and month of onset may be associated with the incidence of CAL in KD patients.

Introduction

Kawasaki disease (KD), which was first reported by Dr Tomisaku Kawasaki in 1967 (1), is a syndrome of unknown cause and causes systemic vasculitis, with symptoms that include persistent fever, bilateral conjunctival congestion, polymorphous exanthema and, alterations of the lip, oral cavity and peripheral extremities (2). It typically affects children under the age of 5 years. Coronary artery lesion (CAL) is the most severe complication of KD and it has been regarded

as one of the major acquired heart diseases in children (3). Therefore, KD has been a major focus in the field of pediatric cardiology research. Although the introduction of intravenous gamma globulin (IVIG) has effectively reduced the rate of CALs, further research is required to ensure early diagnosis and effective treatment of KD (4). Several epidemiologic surveys of KD have been conducted worldwide since 1970's, and various features of the disease have been revealed, such as disease incidence, seasonality, and the rate of CAL (3). KD has been reported in numerous countries with a greatly varying incidence, and the highest incidence of KD has been reported in Japan, followed by other East Asian countries and districts surrounding Japan (3). However, the epidemiology of KD has only been reported in a limited number of regions in China, and to the best of our knowledge, it has not been previously determined in the Inner Mongolia Autonomous Region of China. Therefore, in the present study, a survey was conducted to examine the epidemiologic features of KD in Inner Mongolia between 2001 and 2013.

Materials and methods

Population. A retrospective study of patients treated for the KD in Inner Mongolia between January 1st, 2001 and December 31st, 2013 was conducted. Regardless of ethnicity, patients with KD who were aged <18 years old were identified by the discharge diagnosis code in the records of 17 hospitals providing pediatric medical services in Inner Mongolia, including Inner Mongolia Autonomous Region People's Hospital; Maternal and Child Health Hospital of Inner Mongolia; Inner Mongolia Medical University Affiliated Hospital; Ordos Center Hospital; Chifeng Center Hospital; Affiliated Hospital of Chifeng College; The Second Hospital of Chifeng; Tongliao City Hospital; Affiliated Hospital of Inner Mongolia National University; Hulunbuir City People's Hospital; The First Hospital of Hohhot; Baotou Center Hospital; The Second Hospital of Baotou; Linhe City Hospital; Baogang Hospital of Inner Mongolia; The Fourth Hospital of Baotou; and The First and Second Affiliated Hospital of Baotou Medical College. The medical records of the patients with KD during the 13-year span of the study were reviewed. The 5th revised edition of the diagnostic criteria for KD that was issued by the Japan Kawasaki Disease Research Committee at the 7th International Kawasaki Disease

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Abbreviations: KD, Kawasaki disease; CAL, coronary artery lesion

Key words: Kawasaki disease, epidemiology, incidence

Symposium in 2002 was used for the diagnosis of KD in all cases (2). In brief, the patients included in the study presented at least 5 of the following 6 clinical manifestations, or at least 4 symptoms along with coronary abnormalities documented by echocardiography or coronary angiography: i) Fever persisting for 5 days or longer (including cases in which the fever has subsided before day 5 in response to treatment); ii) bilateral conjunctival congestion; iii) alterations in the lip and oral cavity areas, including diffuse congestion of oral and pharyngeal mucosa, strawberry-colored tongue or reddening of the lips; iv) polymorphous exanthema; v) alterations in the peripheral extremities, such as reddening of the soles and palms, indurative edema at the initial stages, or membranous desquamation at the fingertips during the convalescent stage; and vi) acute nonpurulent cervical lymphadenopathy (5). Patients who did not fulfill the aforementioned criteria, were diagnosed beyond the specified time period or were not residents of the Inner Mongolia region were excluded from the present study.

Survey implementation. The clinical data collected from the eligible patients included the following: Age, gender, ethnic background, location of residence, dates of KD onset and diagnosis, days between symptom onset and hospital visit, clinical signs and symptoms, cardiac and extracardiac manifestations, laboratory examination results (routine blood examination, erythrocyte sedimentation rate and blood chemical tests), echocardiogram results, treatment and outcome.

Statistical analysis. Parametric data are expressed as the mean \pm standard deviation. Nonparametric analysis was performed using Pearson's χ^2 test or Fisher's exact test. Differences between the mean values were compared by t-test or one-way analysis of variance. Single-factor analysis and nonconditional multivariate logistic regression analysis were performed to analyze the risk factors for the development of CAL. A value of $P < 0.05$ was considered to indicate a statistically significant difference. All analyses were performed using SPSS software version 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

Incidence of KD. A total of 597 KD cases were identified in the medical records of the included hospitals within the study period. Of these, 79 cases were excluded through strict quality control, due to not meeting the study criteria. The remaining 518 KD cases were enrolled in the present study population. The number of patients with KD per year, as well as the determined incidence rates in the surveys, are shown in Fig. 1. Based on the Statistical Yearbook data for Inner Mongolia (6), the mean annual incidence rate of KD was 3.55 ± 2.96 per 100,000 children under the age of 5 years between 2001 and 2013, and the incidence displayed an increasing trend over this time period. There were 322 (62.2%) males and 196 (37.8%) females, with a gender ratio of 1.64:1, respectively. The majority of included KD patients were Han Chinese. Three minority groups were represented by 81 cases (15.8%), including 70 Mongolian, 6 Hui and 5 Manchu patients, and these groups were dispersed throughout the surveyed population.

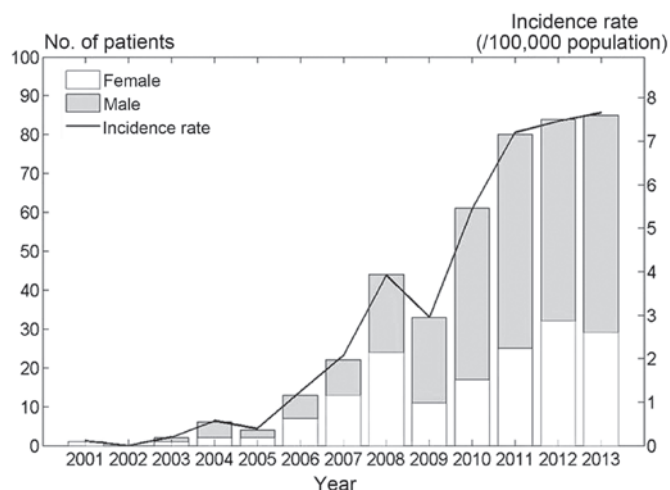


Figure 1. Number of patients with Kawasaki disease and incidence rate in Inner Mongolia (China) by calendar year.

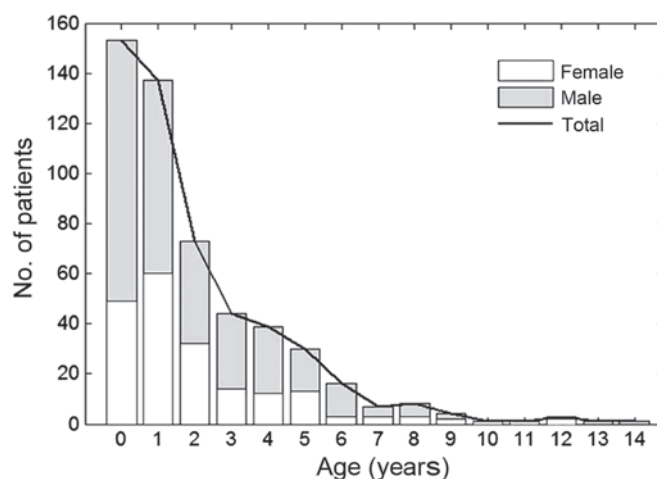


Figure 2. Age distribution of patients with Kawasaki disease in Inner Mongolia (China) between 2001 and 2013.

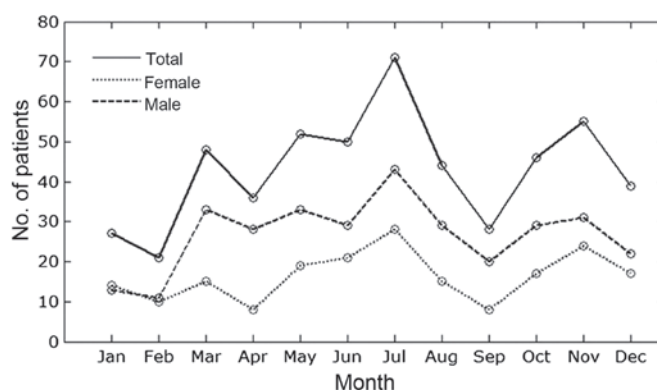


Figure 3. Number of patients with Kawasaki disease in Inner Mongolia (China) according to the month, between the years 2001 and 2013.

Distribution of age at diagnosis of KD. The distribution of age at diagnosis of KD is shown in Fig. 2. The age at diagnosis of KD, which was derived from the date of the first diagnosis (within one month of symptom onset) minus the date of birth,

Table I. Single-factor analysis of the relevant factors for CAL among the included 518 patients with Kawasaki disease in the Inner Mongolia region between 2001 and 2013.

Observed indicator	χ^2 test	P-value
Age of ≥ 5 years	0.245	0.620
Gender	0.099	0.782
Ethnic group	4.657	0.031 ^a
Month of onset	21.040	0.029 ^a
Fever duration of ≥ 5 days	1.010	0.315
White blood cell count of $\geq 12 \times 10^9/l$	0.437	0.508
Hemoglobin level of < 100 g/l	3.274	0.070
Blood platelet count of $\geq 450 \times 10^9/l$	1.334	0.248
Erythrocyte sedimentation rate of ≥ 40 mm/h	1.170	0.279
Creatine kinase-MB level of ≥ 25 U/l	0.528	0.473

^aP<0.05 indicates the observed indicators that were associated with CAL. CAL, coronary artery lesion.

Table II. Nonconditional multivariate logistic regression analysis of Kawasaki disease complicated by coronary artery lesion among the included 518 patients with Kawasaki disease in the Inner Mongolia region between 2001 and 2013.

Factor	Partial regression coefficient	OR	95% CI	P-value
Ethnic group (Han Chinese)	0.736	2.087	1.083-4.02	0.028 ^a
Month of onset (July)	-0.881	0.414	0.199-0.864	0.019 ^a

^aP<0.05. OR, odds ratio; CI, confidence interval.

ranged between 49 days and 14 years (median, 1.42 years). Cases under the age of 1 year and under the age of 5 years accounted for 56.0% (290 cases) and 86.1% (446 cases), respectively, of the patient cohort. The incidence rate was highest among children aged 0-1 years, after which the incidence decreased sharply with increasing age.

Monthly distribution of KD. Trends in the monthly number of patients are shown in Fig. 3. During the survey period, the onset of KD in all patients occurred more frequently in March (48 cases; 9.2%), May (52 cases; 10.0%), July (71 cases; 13.7%) and November (55 cases; 10.6%), whereas it occurred relatively less frequently in February (21 cases; 4.1%). Furthermore, the incidence peak for boys and girls both occurred in July (43 cases, 13.4% and 28 cases, 14.3%, respectively).

Clinical manifestations of KD. Among the main clinical manifestations of patients with KD in the present study, fever persisting for 5 days or longer was the most frequent manifestation (516 cases; 99.6%), followed by changes in the lips and oral cavity (383 cases; 73.9%), conjunctival congestion (355 cases; 68.6%), polymorphous exanthema (334 cases; 64.5%), changes in the peripheral extremities at the initial or convalescent stages (322 cases; 62.1%), and acute nonpurulent cervical lymphadenopathy (321 cases; 61.9%). Other manifestations included perianal desquamation (118 cases; 22.8%), coughing (63 cases; 12.2%), diarrhea (17 cases; 3.3%), and emesis (12 cases; 2.3%). Respiratory system disorders were identified in 186 cases

(35.9%) and liver impairments were observed in 20 cases (3.9%). Mortality did not occur in any of the cases during the acute and subacute stages of the disease.

Echocardiographic findings of KD. Echocardiographic examinations were performed in 501 cases (96.7%) within one month after the onset of KD. Among these patients, abnormal findings were observed in 230 cases (45.9%), including coronary artery ectasia (203 cases; 40.5%), coronary artery aneurysm (2 cases; 0.87%), pericardial effusion (13 cases; 5.7%), mitral regurgitation (24 cases; 4.8%), tricuspid regurgitation (12 cases; 2.4%), patent foramen ovale (11 cases; 2.2%) and patent ductus arteriosus (6 cases; 1.2%). In total, CAL, defined as ectasia or aneurysm, was observed in 40.9% of all cases undergoing echocardiographic examination. In certain patients, various cardiac abnormalities were identified simultaneously.

Therapies and prognosis. Treatment with intravenous immunoglobulin infusion (human freeze-dried low-pH intravenous gamma globulin; Biochemical Product Institute of Ministry of Public Health, Chengdu, China) was performed in 433 patients (83.6%) within one month after KD onset. The regimens administered to patients included 400 mg/kg/day for 5 consecutive days in 6 cases (1.4%), 1,000 mg/kg twice in 156 cases (36.0%), 2,000 mg/kg once in 70 cases (16.2%), and an irregular dose in 154 cases (35.6%). Among these, the treatment regimen of 1,000 mg/kg/day twice was adopted more frequently. No adverse effects due to this treatment were identified in the

current study. Besides intravenous immunoglobulin therapy, aspirin was administered orally in 455 cases, and steroids were administered in 31 cases. In total, 310 patients were improved after treatment and were discharged from the hospital, whereas 14 patients were transferred to a higher level hospital and 194 patients were discharged without medical advice due to various limitations, such as financial difficulties and poorly conditioned local medical institutions.

Risk factors of CAL. Single-factor analysis of risk factors relevant to CAL incidence was conducted with a focus on patient age, gender, ethnic group, month of onset, duration of fever (≥ 5 days), white blood cell count ($\geq 12 \times 10^9/l$), hemoglobin level (< 100 g/l), blood platelet count ($\geq 450 \times 10^9/l$), erythrocyte sedimentation rate (≥ 40 mm/h) and creatine kinase-MB level (≥ 25 U/l). The results of the analysis indicated that ethnic group and month of onset were associated with the occurrence of CAL, as shown in Table I.

Furthermore, nonconditional multivariate logistic regression analysis was conducted for a single factor that was associated with CAL in KD. The Han Chinese ethnic group and July as the month of onset were selected for the multivariate logistic regression equation, and the corresponding P-values were found to be < 0.05 (Table II). These results indicated that KD patients in the Han ethnic group were more likely to be complicated by CAL, whereas KD patients with onset occurring in July were less likely to be complicated by CAL. This may be due to climatic and environmental conditions, or living habits during different months, which may affect incidence; however, the possibility that this association was coincidental cannot be ruled out.

Discussion

KD was first recognized in 1967 (1); however, the etiology of the disease remains unclear. Various researchers have hypothesized that infectious agents may trigger the onset of KD (7,8), however, no certain conclusion can be reached. Therefore, a large-scale epidemiologic survey is required to identify clues regarding the etiology and pathogenesis of KD. Currently, KD has been reported in > 60 countries and districts, including in Asia, Middle East, America, Africa and Europe (3). The incidence rate appears to be the highest in Japan, followed by East Asian countries and districts, such as China, Hong Kong, Taiwan, and Korea, with an increasing trend in numerous countries (3).

According to the results of the present 13-year survey conducted on KD cases between 2001 and 2013, the incidence rate was found to be increasing in Inner Mongolia during the study period, and the latest incidence rate was reported to be 7.7 per 100,000 children in 2013. The increasing trend has also previously been reported in other countries, districts and different regions of China (9-13). However, the awareness of this disease has increased among physicians during the time span, which may affect the accuracy of reported incidences of KD. Therefore, continuous monitoring of KD is important to better understand the incidence trend of this disease.

Regarding the age distribution of patients at onset of KD, the present data demonstrated that the disease predominantly occurred in children under the age of 5 years, which accounted for 86.1% of the KD cases, and the peak age of KD onset was

0-1 years (56.0%). These findings are in consistency with previous reports, while the male preponderance observed in the current study (male to female ratio, 1.64:1) was also comparable with previously studies from other regions of China (5,9-13).

As seasonal variation may be an important epidemiology characteristic of KD (3), the current study also focused on the seasonality of KD. According to the present results, the disease occurred all the year around, but more frequently in March, May to July, and November. The incidence appeared to peak in July, with the lowest point appearing in February. The seasonal distribution of KD occurrence in the present study is similar to that reported in a survey performed in Jilin province in China (5). However, great seasonal distribution discrepancies have been reported in studies involving different countries. For instance, in Japan, the number of patients was highest in January and lowest in October (14). In Korea, the majority of KD cases occurred in June, July and August, followed by December and January (15). In the United States, seasonal peaks in KD occurrence were observed in the winter and spring months (16), whereas in several European countries including England, Denmark and Ireland, there was a similar peak occurrence of KD in the winter months (17-19). Although seasonal distribution has been perceived as an important characteristic of descriptive epidemiology, the reasons for these discrepancies remain unclear. Different climatic and environmental conditions, ethnic group and living habits may possibly contribute to these discrepancies.

In consistency with previous studies (5,10-13), fever persisting for 5 days or longer was the most frequent clinical manifestation of KD, followed by changes in the lips and oral cavity, conjunctival congestion, polymorphous exanthema, changes in peripheral extremities and acute nonpurulent cervical lymphadenopathy. Notably, although perianal desquamation is not included in the diagnostic criteria of KD, it was observed in 22.8% of the cases included in the present study, and a relative higher incidence of perianal desquamation was also showed in several other studies (5,11,20). As a systemic vasculitis, the present study also identified that KD affects multiple systems, including the respiratory and digestive system, and in certain cases, atypical clinical manifestations may lead to the misdiagnosis of KD (21); therefore, increased awareness of the spectrum of the clinical presentation of KD is essential for early diagnosis and treatment.

CAL is the most severe complication and a great health concern in KD patients. The incidence of CAL was reported to be 40.2% in the present survey during the acute stage, which was comparable with the rates reported by Baer *et al* (22) and Zhang *et al* (5). However, the rate reported in the present study was relatively high when compared with that of certain other reports (9,11,13,16,23), which may be due to the delayed diagnosis and treatment as a result of the relatively lower economic level of the Inner Mongolia region. In addition, this inconsistency in CAL incidence may be due to differences in ethnicity and region, as well as discrepancy brought by multifarious diagnostic standards. Besides, regarding risk factors of CAL in patients with KD, the present study indicated that patients in the Han ethnic group were more likely to be complicated by CAL, whereas KD patients whose month of onset was in July were less likely to be complicated by CAL; however, further

studies are required to further investigate the underlying reasons for these observations.

It has been reported that intravenous immunoglobulin treatment is able to significantly relieve clinical symptoms and reduce the rate of CAL; therefore, it has become the main treatment for KD (24-27). In the current survey, 83.6% of the cases received treatment with intravenous immunoglobulin infusion within one month after KD onset. However, the optimal time window, dosage and the mechanism of the pharmacological effects of this treatment remain arguable (27,28), and require further exploration.

There are certain limitations in the current study. Firstly, the retrospective nature of the study and the reliance on data from numerous different centers may affect the accuracy of the study. In addition, certain patients may not be included among the target hospitals for the survey due to misdiagnosis, economic limitations and lack of hospital space or of pediatric departments; the effects of these on the overall results are unlikely to be substantial.

In conclusion, the present study reported that the number of patients and incidence rate of KD in Inner Mongolia tend to increase year by year. The age distribution and clinical manifestations were similar to those reported in previous studies involving different region of China. Furthermore, the present study reported that the onset of KD was more frequent in spring and summer, and a higher incidence of CAL was reported in comparison with other studies. Ethnic group and month of onset were also found to be associated with the incidence of CAL in KD patients. Continues monitoring of KD and further studies focusing on identifying the etiology of KD are required to facilitate early diagnosis and more specific treatment of KD, therefore decreasing its morbidity and mortality rates.

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