Postnatal Risk of Acquiring Kawasaki Disease: A Nationwide Birth Cohort Database Study

Mei-Hwan Wu, MD, PhD[1], Min-Tai Lin, MD, PhD[1], Hui-Chi Chen, PhD[2], Feng-Yu Kao, MS[3], and San-Kuei Huang, MD[3]

Objective To investigate the postnatal risk of Kawasaki disease and coronary complications from a nationwide birth cohort in Taiwan, a country with the third-highest incidence of Kawasaki disease worldwide.

Study design We enrolled children born between 2000 and 2009 with complete postnatal medical care records for 2000-2014 in the Taiwan national database.

Results Out of a total of 2 150 590 live births, we identified 6690 (62.6% boys) patients with Kawasaki disease. The onset was mostly (93.9%) within the first 5 years of life (median, 16 months; 38% during infancy), but was rare within the first 3 months of life. The overall cumulative incidence of Kawasaki disease by age 5 years was 2.78‰ (3.33‰ for boys and 2.17‰ for girls; $P < .001$) and exhibited an increasing trend with birth year (from 2.28‰ for 2000 to 3.67‰ for 2009). The incidence ratio was 1.535 in boys and 1.055 in each increasing year. Kawasaki disease recurred more often in younger patients (cumulative incidence, 2.3% in infants vs 1.7% in children aged 1-4 years). Coronary complications occurred in 16.2% of the patients, including 4 cases of acute myocardial infarction (3 occuring during the acute stage and 1 occurring 5 years later). The probability of a major cardiac event (infarction, undergoing percutaneous coronary intervention or coronary artery bypass grafting, or death) by adolescence was 1.9%.

Conclusions The postnatal risk of Kawasaki disease was 3‰-4‰ and increased with every birth year. Patients with Kawasaki disease are at substantial risk for a major cardiac events during childhood. *(J Pediatr 2017;180:80-6).*

Kawasaki disease is a common systemic vasculitis occurring predominantly in children aged <5 years.[1,2] Dr Kawasaki reported the first case of Kawasaki disease in 1967, and since then, the incidence of Kawasaki disease has shown an increasing trend worldwide.[3-19] Despite advances in immunomodulation and antithrombotic regimens, coronary arterial complications still occur in 10%-15% of patients and may persist as unique Kawasaki coronary artery disease.[1,2,20-23] Considerable racial differences in the epidemiologic profile of Kawasaki disease have been reported, with a higher incidence in Asian populations compared with Western populations.[4-19] These reported incidence data were obtained from nationwide hospital surveys, claims data analyses, and hospital databases. The incidence of Kawasaki disease in Taiwan is the third-highest worldwide and ranges from 50 to 70 per 100 000 children aged <5 years; the only countries with a higher incidence are Japan (264.8/100 000) and Korea (127.7/100 000).[4-7] Previous reports have been based on cross-sectional data, however, and may be limited by a lack of previous history. Studies involving birth cohort databases have yet to be presented.

Since implementation of Taiwan's National Health Insurance program in 1995, which currently covers approximately 99.9% of the population (23 million adult patients and approximately 5 million pediatric patients), nearly every child in Taiwan receives complete medical services. Thus, a nationwide birth cohort from Taiwan with complete postnatal data for >5 years is appropriate for investigating the risk of Kawasaki disease since birth, as well as the corresponding outcomes. Using this cohort, we examined the epidemiologic profile of Kawasaki disease in Taiwanese children, focusing on the postnatal risk of Kawasaki disease and its coronary sequelae.

Methods

Complete health care records of patients born between January 1, 2000, and December 31, 2009, were retrieved from the National Health Insurance Database between January 1, 2000, and December 31, 2014. These patients constituted a 2000-2009 birth cohort with at least 5 years of postnatal follow-up. Patients with a diagnosis of Kawasaki disease, based on *International Classification of Diseases, Ninth*

AMI	Acute myocardial infarction
CABG	Coronary artery bypass grafting
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IVIG	Intravenous immunoglobulin
PCI	Percutaneous coronary intervention

From the [1]Department of Pediatrics, National Taiwan University Hospital, National Taiwan University Children's Hospital and Medical College, National Taiwan University, Taipei, Taiwan; [2]Genomics Research Center, Academia Sinica, Taipei, Taiwan; and [3]Taiwan Administration of National Health Insurance, Taipei, Taiwan

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Revision, Clinical Modification (ICD-9-CM) code 446.1, were selected for analysis. Each health record had a scrambled identification number and contained such information as the patient's date of birth, date of hospital visit, sex, type of visit (admission or outpatient department visit), diagnosis and treatment codes, and reimbursement fees. All patients admitted to a hospital in Taiwan with the major diagnosis of Kawasaki disease were enrolled. Intravenous immunoglobulin (IVIG) therapy was defined as receipt of medication with the therapeutic classification code J06BA02 and a reimbursement code for IVIG. Patients who received medical care with a major diagnosis of Kawasaki disease in an outpatient clinic only were enrolled only when they had coronary complications.

Recurrence was defined as readmission with a main diagnosis of Kawasaki disease and receipt of IVIG therapy. Two admissions occurring within 30 days were considered to represent the same acute stage of Kawasaki disease.

Identified patients were followed for any complications or interventions up to December 31, 2014. Coronary complications were defined as the occurrence of any of the following conditions: acute myocardial infarction (AMI; ICD-9-CM code 410), old myocardial infarction (ICD-9-CM code 412), angina pectoris (ICD-9-CM code 413), and other forms of chronic ischemic heart disease (ICD-9-CM code 414, other than code 414.11). Coronary aneurysm was defined as the diagnosis of a coronary aneurysm on the basis of ICD-9-CM code 414.11. Cardiac catheterization was defined as reimbursement for any of the following treatment codes: 18020B, 18021B, 18022A, 18022 B, 18027B, 97501K, 97502A, 97502B, 97503B, 97506K, 97507A, and 97508B. Percutaneous coronary intervention (PCI) was defined as reimbursement for any of the following treatment codes: 33076B, 33077 B, 33078 B, 97511K, 97512A, 97513A, 97513B, 97516K, 97517A, 97518B, 97521K, 97522A, and 97523B. Surgical coronary artery bypass grafting (CABG) was defined as reimbursement for any of the following treatment codes: 68023A, 68023B, 68024A, 68024B, 68025A, 83064A1, 97901K, 97902A, 97902A, 97903B, 97906K, 97907A, 7908B, 97911K, 97912A, 97913B, 97916K, 97917A, and 97918B. Acute mortality was defined as death during discharge or within 1 month of Kawasaki disease onset. Survival status was further confirmed by evaluating the insurance status on December 31, 2014.

Statistical Analyses

All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, New York). The numbers of sex-specific newborns between 2000 and 2009 were adopted from the Statistical Yearbook of the Department of Statistics, Ministry of the Interior. The χ^2 test was used to analyze the associations between categorical variables. The Fisher exact test was used when the number in the cell was <5. Multivariate logistic regression was then applied to identify the risk ratios for the incidence rate, as well as the predictors for Kawasaki disease recurrence and coronary complications. All *P* values were 2-sided, and statistical significance was defined as $P < .05$. Kaplan-Meier analysis was used to estimate the overall event-free rate for major cardiac events.

Results

Figure 1 (available at www.jpeds.com) presents a flowchart of the study procedure. Between 2000 and 2009, out of a total of 2 150 590 live births in Taiwan, we identified 8433 patients with Kawasaki disease. Patients who did not receive IVIG treatment during the acute stage and did not have any coronary complications were excluded. Thus, we enrolled 6690 patients (62.6% male) who received IVIG treatment during the acute stage (6426; 96.1%) or had coronary complications (264; 3.9%) as patients with definite Kawasaki disease and assigned them to the Kawasaki disease cohort. The follow-up period of the Kawasaki disease cohort was 10.45 ± 3.02 years, with total follow-up of 70 146 person-years.

Most of the patients (93.9%) experienced onset of Kawasaki disease within the first 5 years of life, more than one-third (38%) during infancy (**Figure 2**, A). However, onset was rare in infants aged <3 months (7.2% of those with onset during infancy), and was extremely rare during the neonatal period (0.04% of those with onset during infancy) (**Figure 2**, B). The median age of onset was 16 months (mean age, 22.3 ± 20.4 months), and it did not differ between boys and girls.

Cumulative Incidence of Kawasaki Disease by Age 5 Years

In the entire cohort, the overall cumulative incidence of Kawasaki disease by age 5 years was 2.78‰ (95% CI, 2.71‰-2.85‰) and was significantly higher in boys compared with girls (3.33‰; 95% CI, 3.23‰-3.43‰ vs 2.17‰; 95% CI, 2.08‰-2.26‰; $P < .001$). To elucidate the incidence trend in association with birth year, we calculated the cumulative incidence of Kawasaki disease by age 5 years in each birth year cohort (**Figure 3**, A). We observed a significant increasing trend in cumulative incidence by age 5 years with birth year. The cumulative incidence by age 5 years was 2.28‰ in the 2000 birth year cohort, and steadily increased to 3.67‰ in the 2009 birth year cohort.

We grouped the places where the patients received medical care into 6 regions, according to administrative data: Taipei metropolitan, northern Taiwan, central Taiwan, central-to-southern Taiwan, southern Taiwan, and eastern Taiwan. Although the male:female and trend of increasing association with birth year were similar, the cumulative incidence of Kawasaki disease by age 5 years in eastern Taiwan was only one-half the cumulative incidences in other parts of Taiwan (**Figure 3**, B).

Age-Specific Incidence of Kawasaki disease

The annual incidence of Kawasaki disease in children aged <5 years was 55.9 (boys, 67.1; girls, 43.7) per 100 000 person-years. The annual age-specific incidence peaked during infancy (119.4 per 100 000; boys, 148.8; girls, 87.2) (**Figure 4**, B; available at www.jpeds.com). The incidence gradually dropped to 83.7 per 100 000 in children aged 1 year, 42.1 per 100 000 in children aged 2 years, and 15.4 per 100 000 in children aged 4 years (**Figure 4**, B). After age 5 years, the incidence