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Epidemiologic Study of Kawasaki Disease and Cases Resistant to IVIG Therapy in Thailand

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SUMMARY The incidence of Kawasaki disease (KD) in Thailand has never been studied before. We reviewed the data from the National Registry of Thai Children who had KD between 1998-2002 to evaluate the incidence of KD and cases resistant to treatment with intravenous immunoglobulin (IVIG). Resistance to IVIG was defined as remaining febrile at least 48 hours after initial IVIG therapy. There were 710 KD patients in the registry. The incidence of KD was from 2.14 to 3.43 cases per 100,000 children aged 0-5 years. During the acute phase 15.6% of 435 patients were considered as resistant cases. Resistant cases of KD in Thai children are quite common (15.6%) even after IVIG treatment. We found that patients who had high white blood cell counts (> 16,500 cells/mm^3) had a higher likelihood of being resistant.

Kawasaki disease (KD) is a systemic vasculitis characterized by fever, mucocutaneous manifestations, and musculoskeletal changes with its most serious effects on the heart, in particular, the coronary arteries.[1] If not treated, up to 15% to 25 %[2] of patients may develop coronary artery aneurysm (CAA). A previous study also showed endothelial dysfunction in KD.[3] In Japan, KD can also present with long term sequelae as young adults with coronary artery disease.[4] After the publication of the successful treatment of KD using intravenous immunoglobulin (IVIG) in Japan,[5] a US multi-center study group was formed and two trials of high dose IVIG therapy for acute KD were conducted.[6,7] The results of these trials have established that IVIG plus aspirin lowered the frequency of CAA from 20% to 3%-5%. In addition, a single dose (2 g/kg) of IVIG resulted in a rapid improvement of acute systemic symptoms. A meta-analysis was conducted in 1995 which confirmed these findings.[8] However, several studies showed that higher frequencies of CAA between 10-15% were encountered even after IVIG treatment. Several cases of KD (up to 23%)[9-12] were unresponsive to the initial treatment with IVIG. The majority of these patients continued to have fever and other systemic symptoms after initial IVIG treatment.

In Thailand over the past few years we have seen several cases of KD which were unresponsive to

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initial IVIG treatment.[13] In 2002 and 2003, the National Registry for Kawasaki Disease was established. We hypothesized that all of the Kawasaki disease patients at any point of time would be referred for echocardiography examination. Most of the echocardiography in children for coronary imaging was done by pediatric cardiologists in large medical centers, both public and private. The centralized database was set up at Siriraj Hospital. All major medical schools and large medical centers in the country that had pediatric cardiologists were enrolled in the study group with seven sites covering each region of Thailand. The majority of the large medical centers also received referrals of patients in the nearby provinces. We retrospectively analyzed data of all children who had been newly diagnosed with KD including also data from an echocardiography database. The private hospital data were collected by one of the investigators (BP). We tried to determine the incidence of newly diagnosed KD per child aged 0 to 5 years old by using also the statistics from the National Statistics Office website. We also looked for variables associated with initial IVIG treatment failure.

MATERIALS AND METHODS

In general all KD patients were referred to pediatric cardiologist for evaluation of cardiac involvement either during acute or late presentation. The National Registry was set up to include data from all major referral cardiac centers from all regions of Thailand. Patients who fulfilled the criteria for KD established by the American Heart Association[14] who were admitted between January 1998 to December 2002 were enrolled in our study. We diagnosed patients who had incomplete manifestations if they did not reach 4 out of 5 criteria based on evidence of cardiac involvement from echocardiographic examination. The data analysis included demographic data, detail on days of fever, routine laboratory analysis including a complete blood count (CBC), platelet count and erythrocyte sedimentation rate (ESR).

The number of days of fever was counted including the first day of fever. The management of KD in Thailand generally includes a single dose of IVIG (2 g/kg) over 12 hours with aspirin (80-100 mg/kg) for a minimum of seven days or until the fever had subsided. Then the aspirin dosage was lowered to 5 mg/kg. Once initial echocardiogram evidence of coronary artery involvement was found, a repeat echocardiogram was done within 7-10 days and at 14 to 21 days after the initial diagnosis. The occurrence of coronary artery aneurysms reported here was taken from all of the results of the echocardiograms performed within one month of the acute illness. We specifically report the presence of CAA based on published criteria from the American Heart Association[15] and from the Research Committee sponsored by the Japanese Ministry of Heath and Welfare.[16] Resistant cases were defined as patients with fever more than 48 hours after initial IVIG treatment during the acute phase.

The incidence of KD in each year was compared to the number of children aged 0-4 years (under 5 years old) from the National Statistics Office, Ministry of Information and Communication Technology, Thailand.

Statistical analyses

Descriptive analysis was performed on all data. The frequency of resistant cases in each year was calculated. The resistant cases were analyzed to define any predictive factors. Sensitivity and specificity were determined using a receiver operating curve (ROC) to define the cutoff level for prediction of resistant cases. SPSS 11.0 (Chicago, U.S.A) was used.

RESULTS

There were 710 patients with KD during the study period. Out of these only 622 patients had obtainable echocardiography results (up to one month after the initial illness). The average age of the patients was 26.8 ± 22 months old (range = one month to 15 years). The average weight was 12.4 ± 5 kg (4.2 to 46 kg). There were 59.7% males. Five hundred and twenty-nine patients were diagnosed during the acute phase or during readmission due to recurrent fever. The average days of fever before diagnosis were 7.4 ± 3.5 days (2-30 days). The frequency of symptoms as criteria for diagnosis were as follows: rashes (92.6%), conjunctivitis (84.5%), oral mucosal involvement (82.9%), change in extremities (74.8%), and cervical lymphadenopathy (54.8%). There were 62.1% of patients who had a classic presentation of

at least 4 out of 5 criteria for diagnosis of Kawasaki disease. Among patients who did not reach 4 criteria, 16.6% had 3 criteria and 5.6% had 1-2 criteria. There were 435 patients who were treated with IVIG during their acute phase. All of them had a single dose (average of 2 gm/kg) of IVIG.

The incidence of KD patients in each year was compared to number of children aged 0-4 years old from the National Statistics Office of Thailand as in Table 1. Over all the incidence of KD ranged from 2.14 to 3.43 cases per 100,000 children aged 0 to 5 years old.

Patients who failed to respond to single dose IVIG

Patients who continued to have fever more than 48 hours after the treatment were considered as resistant cases. Out of 529 patients who presented during the acute phase, there were 68 patients (15.6%) who continued to have a high fever after initial IVIG treatment. There were 8 patients who were treated with methylprednisolone. However, since the decision to use a second dose of IVIG depended on each individual institute, only 34 patients had repeated doses (second and third) of IVIG. The percentage of resistant cases among all patients in the registry ranged from 6.9% to 12%.

There were no observed differences in age, gender, weight, an duration of fever presented before the IVIG treatment between patients who were responsive or resistant to IVIG. Initial bedside laboratory observations, including complete blood count, did show a significant difference between the two groups. Patients who were resistant to IVIG treatment had a higher white blood cell count (p = 0.003), higher ESR (p = 0.038) and a lower hemoglobin (p = 0.009). The receiver operating curve was performed among these three parameters. Only a high white blood cell count of over 16,500 cells/mm^3 was associated with a higher chance of resistance with sensitivity and specificity of 75% and 65%, respectively (Fig. 1).

Coronary artery aneurysm (Fig. 2)

There were 529 patients who were treated during the acute phase of KD. Out of this group only 432 patients (82.2%) were treated with IVIG. The other 94 patients were treated with only aspirin. The frequency of CAA during the acute phase (within one month) was 23.4 % in the aspirin group and 14.5% in the IVIG group who had a response with no fever within 48 hours. For resistant cases (patients who had IVIG and did not respond within 48 hours which required second dose of IVIG), the frequency of CAA was 26.5%.

DISCUSSIONS

Kawasaki disease was first reported in Thailand in 1976.[17] In 1995, there was an initial report of coronary artery involvement in 25 patients with KD.[18] However, IVIG was not routinely given as a single dose regimen until 1995. Between 1998 and 2002 the national registry was established in order to collect all of the information on clinical manifestations of KD in Thai patients. Although the nature of the study was retrospective, we were able to draw some conclusions about the incidence of KD in Thai children and the number of patients who were resis-

Table 1 Comparison of the incidence of Kawasaki disease and the percentage of resistant cases (during acute phase) from 1998 to 2002 from national registry

	1998	1999	2000	2001	2002
New Kawasaki cases	182	148	111	129	133
Resistant cases	17	11	8	9	16
Number of children (aged 0-5 years in thousands)	5.305	5.246	5.185	5.155	5.116
Incidence of KD per 100,000 children (aged 0-5 years)	3.43	2.82	2.14	2.50	2.59
Percentage of resistant cases	9.34%	7.43%	7.21%	6.98%	12.03%

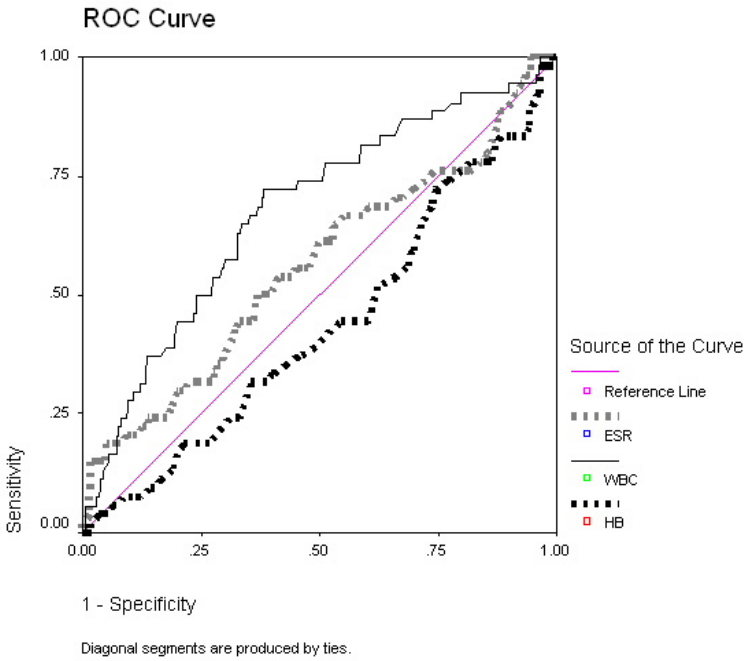

Fig. 1 Receiver operation curve of three predictor factors; from top to bottom, white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and hemoglobin (HB).

tant to IVIG treatment.

The incidence of KD ranged from 2.14 per 100,000 of children age 0-5 years old to 3.43 per 100,000 from 1998 to 2002. The incidence was lower than those previously reported from Japan, China, Taiwan and U.S.A.[19-24] We believe that the data from Thailand might be underreported. The reported incidence for children < 5 years in U.S.A. showed that the number increased from 8.1:100,000 in 1988 to 18.5:100,000 in 1997.[24] The increasing recognition of KD diagnosis and awareness of the need for referral or hospitalization by clinician may have contributed to the increasing incidence of KD. The reported incidence of KD in Thailand may increase in the future for the same reason.

The ratio of resistant cases to total cases of KD in our study ranged from 6.9% to 12.0% in each year which is comparable to the previous findings of Sundel *et al.*[11] in 1993 (10%), Burns *et al.*[9] in 1998 (7.8%), Wallace *et al.*[12] in 2000 (23%) and Fukunishi *et al.*[10] in 2000 (15.9%). It has been pointed out by the U.S./Canadian Kawasaki Study Group[9] that the retreatment rate for patients with persistent or recrudescent fever after initial IVIG therapy varies from 25% to 100% among participating centers. The time duration before the second IVIG dose was given was different in each study. If the fever persisted, those who had divided doses (over four or five days) of IVIG[10] generally required a longer period of time before the second dose of IVIG was given when compared to those with a single dose IVIG regimen.[9,11,12] A lower hemoglobin value (< 10 g/dl), a higher C-reactive protein > 10 mg/dl and LDH > 590 IU/l were risk factors for unresponsiveness to IVIG treatment described by Fukunishi *et al.*[10] As in the previous studies,[9,10,12] we found no association between age or gender of patients who failed the initial IVIG treatment.

Earlier published reports observed that the likelihood of coronary aneurysm was higher among patients with a greater severity of vasculitis, as reflected by a longer duration of fever and evidence of a more inflammatory response (acute phase features [ESR, CRP]).[12,25,26] Analysis of data obtained early in the course of the disease suggested that there was a higher risk in patients of younger age, of male gender, with elevated CRP with high absolute band

counts.[9,26] The Harada score was developed in the early 1990s to select patients who were at higher risk of developing CAA. This scoring system was weighted towards younger males with anemia (Hematocrit < 35%), white blood cell counts (> 12,000 cells/mm^3), low albumin level (< 3.5 g/dl) and a positive C-reactive protein. Since our current treatment is to give a single dose of IVIG (2 g/kg) to every KD patient in the acute phase, we did not use the Harada score in our study. Later, Beiser *et al.*[27] developed and prospectively validated a sequential risk classification for CAA among IVIG treated patients. The risk factors calculated were high neutrophil count with high band/neutrophil count ratio, prolonged fever and male gender, which were also found in our study.

The purpose of this report was to identify the incidence of KD in Thai children. The national registry also showed that the frequency of resistant cases ranged from 6.9% to 12%. The analysis of predictor for resistant case was to help our pediatricians to identify quickly children with a higher risk of initial single dose IVIG treatment failure by some quick investigations (higher white blood cell count [> 16,500 cells/mm^3]). The frequency of cardiac evaluation and testing may be stratified by a predicted risk of IVIG failure. There have always been differences in the clinical manifestations of KD patients found in different studies as pointed out by a previous meta-analysis.[8] Since the real etiology of KD is unknown, these differences might also arise from the racial heterogeneity in each study.

Certain limitations to this retrospective review should be noted. The true incidence of KD in Thai children is not known. Criteria for IVIG retreatment and brand name were not standardized. We used American Heart Association criteria for the diagnosis of CAA.[15,16] However, as pointed out in a previous study, other imaging studies such as multislice spiral computed tomography can also demonstrate coronary artery stenosis.[28] Furthermore, it was found that among patients, judged by having normal coronary arteries on echocardiogram, 27% were found to have coronary dilation more than two stan-

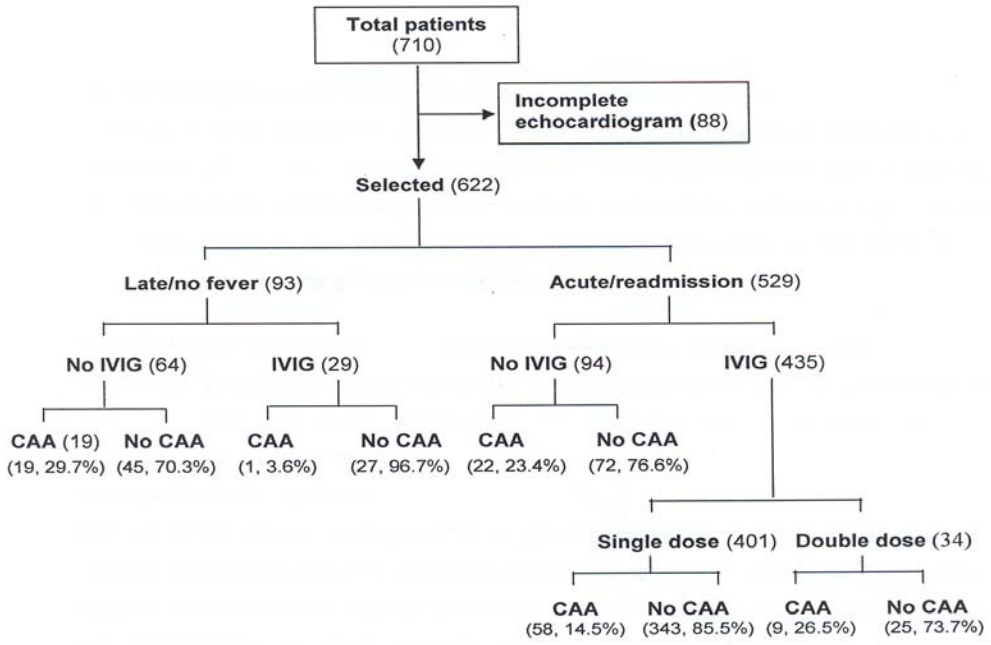

Fig. 2 Diagram showing number of patients in the National Registry. Late/no fever, patients who presented to physicians after the fever had subsided or during the peeling stage; IVIG, intravenous immunoglobulin; CAA, coronary artery aneurysm; single dose, received only one dose of IVIG; double doses, received more than one dose of IVIG.

dard deviations above the expected mean value adjusted for body surface area.[29] Thus, the frequency of the occurrence of coronary artery abnormalities may be underestimated.

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