A Retrospective Cohort Study of Kawasaki Disease in Hue Central Hospital for 10 Years (2010–2019)

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Abstract

INTRODUCTION: Kawasaki disease (KD) is an acute self-limited systemic vasculitis of unknown etiology which affects mainly children <5 years of age. If the disease is left untreated, it can lead to serious complications such as inflammation of the blood vessels.

AIM: We aim to evaluate the clinical and laboratory findings and response to therapy of KD at Hue Central Hospital.

METHODS: This is a retrospective study of patients with KD at Pediatric Center of Hue Central Hospital between January 2010 and December 2019. Clinical and laboratory examinations as well as the echocardiograms finding were analyzed.

RESULTS: All patients were under 5 years old, in which boys were more than girls. Fever lasting over 5 days, changing in the mouth mucosa, and peripheral extremities were seen in all patients. About 73.2% had bilateral conjunctivitis and 78.0% had rash. About 42.3% of patients had cervical lymphadenopathy. Laboratory findings were noted with 84.5% of patients had hyperleukocytosis (>12,000/mm³), 76.2% of patients had high serum C-reactive protein (CRP) levels (>100 mg/dl), 56% of patients had erythrocyte sediment rate >60 mm in the 1st h, and 34.5% of patients had thrombocytosis (platelet count >500,000/mm³) at the time of diagnosis. About 26.2% of patients had coronary artery lesions. Most patients (84.4%) had good outcome since the first dose of gamma-globulin and 13% of patients needed the second dose. There was a significant correlation between coronary artery abnormalities and no or late treatment of gamma-globulin.

CONCLUSION: KD was very common in children under 5 years old with the high rate of coronary artery lesion. Treatment with gamma-globulin on or before 10 days of fever resulted in better coronary outcomes and decreased the total length of time of clinical symptoms.

Introduction

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, was first described in Japan in 1967 by doctor Tomisaku Kawasaki [1]. It has been reported in almost every country of the world, particularly it occurs most commonly in children of Asian descent [2]. Up to 25% of untreated children will develop coronary artery dilatation and may lead to ischemic heart disease, myocardial infarction, or even sudden death [3], but therapy with intravenous immunoglobulin (IVIG) and aspirin within the first 10 days of fever onset reduces the prevalence of coronary artery abnormalities to approximately 5% [4].

In Vietnam, KD was first reported at the National Pediatric Hospital in 1995 and has been popular in almost parts of the country recently. Although no overall data of the prevalence of KD in the whole of Vietnam were established, some sporadic studies showed the rate of cardiovascular abnormalities in KD up to 39.2% [5].

Diagnosis is made difficult by the fact that these symptoms are not usually all present at the same time; the only persistent symptom is fever [6]. Furthermore, it is commonly misdiagnosed as a viral exanthem. Symptoms that point to a diagnosis other than KD include exudative conjunctivitis, exudative pharyngitis, generalized (rather than cervical) lymphadenopathy, discrete intraoral lesions, and a bullous or vesicular rash [6]. Therefore, we aim to evaluate the clinical and laboratory findings and response to therapy of KD in Hue Central Hospital.

Methods

This is a retrospective study of patients with KD at Pediatric Center of Hue Central Hospital between January 2010 and December 2019. The study was approved by the Research Ethics Committee of Hue Central Hospital (IRB No.: 01012019/HCH) and the informed consent was waived.

The study evaluated 168 patients having KD diagnosed in accordance with the American Heart Association (AHA) criteria [7].
Complete KD is defined as having fever of ≥5 days with at least four of the five principal clinical signs:

1. Bilateral conjunctival injections
2. Changes in the lips and oral cavity
3. Polymorphous exanthema
4. Changes in the peripheral extremities, and
5. Acute non-purulent cervical lymphadenopathy.

Incomplete KD was defined as having fever of ≥5 days with three or fewer principal signs, with or without cardiac lesions once other KD-like diseases with similar findings.

Both complete KD and incomplete KD were included in the study. Patients who lost of follow-up within the 1st month post-treatment were exclusive.

Clinical and laboratory examinations, as well as the echocardiograms, were performed at least twice during hospitalization at presentation and within 1 month after discharge. Echocardiography was performed by the same pediatric cardiologist and using the same echo-Doppler apparatus (Philips Evisor).

Coronary artery lesions were defined as ectasia when there was coronary arterial dilatation >3 mm in children that were younger than 5 years or ≥5 mm in children that were 5 years or older, or when the diameter was >1.5 times the size of the adjacent coronary artery [8].

**Treatment protocol**

Patients received IVIG (2 g/kg over 12 h) along with high-dose aspirin (100 mg/kg/day divided into four doses) during the acute phase, followed by low-dose aspirin (10 mg/kg/day), after fever subsides for 48–72 h, for 6–8 weeks [9].

**Statistical analysis**

All calculations were performed using the SPSS ver. 16 (SPSS Inc., Chicago, IL, USA). Results are presented as mean ± standard deviation for quantitative variables and percentages (%) for qualitative. The Pearson’s Chi-square test was used for categorical variables. p < 0.05 was considered statistically significant.

**Results**

A total of 168 patients were enrolled in our study. Of these cases, 111 (66.1%) were boys and 57 (33.9%) girls with the male-to-female ratio = 1.95:1. The mean age was 9.6 ± 4.1 months (range from 4 months to 5 years). Table 1 shows the age distribution of the patients with KD. Most patients were referred to the hospital during March, April, and July (Figure 1).

![Figure 1: Yearly distribution of the Kawasaki disease patients](image)

The most common sign was fever, oral mucosal changes, and changes in extremities followed by polymorphous exanthem and conjunctivitis. The mean body temperature at diagnosis was 38.6 ± 0.9 (°C) after a duration of fever for 7.9 ± 2.9 days since onset. Fever stopped in 1.8 ± 0.7 days after treatment with IVIG. Table 2 shows the clinical manifestations of KD patients.

![Table 2: Clinical manifestations of KD patients](image)

Laboratory findings of the children are summarized in Table 3. Most patients had high erythrocyte sediment rate (ESR) and white blood cell (WBC) with predominance of neutrophils, as well as high platelet and C-reactive protein (CRP). One week after treatment with IVIG, all the disease blood test markers moved to be normalized significantly.

Most patients (130, 84.4%) stopped fever after a single dose of IVIG, but there were 24 patients who need the second dose of IVIG.

Echocardiographic abnormalities were found in 51 (30.3%) patients. Cardiac abnormalities consisted of aneurysm of coronary artery (44 patients), pericardial effusion (5 patients), and mild mitral regurgitation (2 patients). Table 4 shows the characteristics of these abnormal coronary arteries. There was a significant correlation between coronary artery abnormalities and no or late treatment of IVIG (Table 5).
Table 3: Laboratory findings of KD patients at diagnosis and 1 week after treatment

| Laboratory findings | At diagnosis (n=168) (%) | 1 week after treatment (n=168) (%) | p-value |
|---------------------|--------------------------|-----------------------------------|---------|
| Hemoglobin <10 g/dl | 147 (87.5)               | 111 (66.1)                        | <0.001  |
| Hematocrit <35 g/dl | 146 (88.9)               | 120 (71.4)                        | <0.001  |
| White blood cell >12×10^3/mm^3 | 142 (84.5) | 40 (23.8)                        | <0.001  |
| Neutrophil >70%    | 33 (19.6)                 | 3 (1.8)                           | <0.001  |
| Platelet count <350×10^3/mm^3 | 44 (26.2)  | 12 (7.1)                         | <0.001  |
| Platelet count >500×10^3/mm^3 | 58 (34.5)  | 90 (53.6)                        | <0.001  |
| Erythrocyte sediment rate >60, mm/h | 94 (56.0) | 62 (36.9) | <0.001 |
| C-reactive protein >100 mg/l | 128 (76.2) | 30 (17.9) | <0.001 |
| Alkaline transaminase >100 U/l | 12 (7.1)   | 10 (6.0)                         | 0.8517  |
| Aspartate aminotransferase >100 U/l | 16 (9.5)    | 12 (7.1)                       | 0.9488  |
| Albumin <35 g/dl   | 54 (32.1)                 | 28 (16.7)                        | <0.001  |

KD: Kawasaki disease.

Table 4: Characteristics of coronary artery abnormalities in KD (n=44)

| Coronary artery abnormalities (n=44) | Right coronary artery | Left coronary artery | p-value |
|-------------------------------------|-----------------------|----------------------|---------|
| Frequency (n, %)                     | 25 (14.6)             | 44 (26.2)            |         |
| Diameter (mm)                       | 4.1 ± 1.1             | 3.9 ± 1.2            |         |

KD: Kawasaki disease.

Table 5: Correlation between coronary artery abnormalities and IVIG treatment

| Coronary artery abnormalities (n=44) | Coronal artery abnormalities (n=124) | p-value |
|-------------------------------------|-------------------------------------|---------|
| IVIG untreated                      | 8 (18.2)                            | 6 (4.8) | 0.0143 |
| Late IVIG (after 10-day fever)      | 26 (59.1)                           | 28 (22.6) | <0.001 |
| IVIG: Intravenous immunoglobulin    |                                     |         |

Discussion

Since the first report of KD in the early 1960s in Japan, the disease has now seen almost every country of the world, particularly it occurs most commonly in children of Asian descent [2]. Although no overall data of the prevalence of KD in the whole of Vietnam were established, some sporadic studies showed the clinical features, laboratory investigation, and the heart lesion in patients with KD [5].

KD almost always affects children. Most patients are under 5 years old. Boys develop the illness more often than girls [2]. In our study (Table 1), 100% of children were under 5 years old, of which 60.2% were under 1 year old. Boys were nearly 2-fold more than girls. This difference by sex was seen in almost previous reports [10], [11], [12], [13]. Data from 399 patients over the 10-year study period were analyzed by Sánchez-Manubens [14], revealing that 233 (58.4%) had complete KD, 159 (39.8) incomplete KD, and 7 (1.7%) were considered atypical KD. The mean annual incidence was 3.5/105 children <14 years old and 8/105 children <5 years old (mean age 37 ± 33 months, range 1.3–191.3). KD was more frequent in boys (59.6%, p < 0.001). Outside of the tropical region, CIMAZ from Italy showed the same result with the disease peaked in the first 2 years of life, with 85.5% of cases under 5 years. Male/female ratio was 1.4:1. The incidence rate was 5.7/100,000 children 0–14 years old and 14.7 for children younger than 5 years. The incidence had a seasonal distribution, with higher incidence in spring [15]. Similarly, Saundankar from Australia reported that male-to-female ratio was 1.7:1 and the median age was 3.8 years [16].

The clinical manifestations of KD in Hue Central Hospital were very similar to those shown in other studies [14], [15], [17]. Fever persisting for 5 days or longer was still the most frequent clinical manifestation of KD followed by changes of lips and the least frequent symptom was acute non-purulent cervical lymphadenopathy [18].

The clinical diagnosis of KD can be challenging and laboratory testing can help the clinician evaluate the degree of inflammation and can aid in the diagnosis of incomplete KD as outlined by the AHA guidelines [7]. However, a clear understanding of the dynamic nature of these laboratory values is critical to this process. Here, we have comprehensively defined the evolution of laboratory values overtime in KD subjects before and after IVIG treatment.

Children with KD typically have leukocytosis. Many children have a normocytic normochromic anemia and platelet counts are usually elevated by the end of the 1st week of illness with counts exceeding 1 million/mm^3 in some cases. Inflammatory markers are elevated in nearly all patients with KD. Measurements of the ESR are helpful in assessing the degree of inflammation at diagnosis and before IVIG administration. The analytical values of our patients were also similar to those previously described [18]. In his original paper describing the first 50 cases of KD, Dr. Kawasaki noted that both the ESR and CRP were elevated during the initial presentation and became normal “within 3–4 weeks” although “the timing for resolution was not the same” with the CRP returning to normal earlier in the course of illness [19]. There was also a “tendency toward” a high WBC and “various degrees of left shift observed in 41 of the 50 subjects,” a “mild, transient elevation… of serum ALT,” and Coombs negative anemia for 34 of 35 cases during the initial presentation [19]. Our laboratory data in Table 2 were similar to those results.

In the study of Tremoulet et al. [20], many subjects who developed coronary artery abnormalities were also IVIG resistant and received two doses of IVIG, a fact which could explain the increased ESR in the subacute and convalescent phases. However, a comparison of the convalescent ESR of IVIG resistant versus responsive KD subjects with aneurysms did not show a difference between the groups, suggesting...
that the higher ESR in subjects with aneurysms was due to more inflammation rather than an effect of the second dose of IVIG. Failure to normalize markers of inflammation in the convalescent phase suggests that a subset of patients with aneurysms has persistent inflammation that is not well controlled by standard therapy. In our study, none of IVIG resistant was found, but there were 24 (14.3%) patients need the second dose of IVIG. One week after treatment with IVIG, all the disease blood test markers moved to be normalized significantly.

The percentage of coronary dilation in our series was similar (29.2%) to that in other series that describe an incidence around 30% of children by Z-score criteria (Z>2), even when treated with high-dose IVIG regimens within the first 10 days of illness [7]. From a total of 625 children with KD in the study of [21], coronary aneurysms were detected in 60 cases (9.6%), and we identified as primary risk factors associated with their development, the presence of anemia; child’s height below than 103 cm, maximum platelets >900,000/mm³, the total duration of fever >10 days, and the duration of fever >8 days before treatment. In our series, resistance to IVIG treatment was found in more than 15% of the cases, with the development of aneurysms being more frequent in those cases. In the study of Sánchez-Manubens [14], patients with IVIG non-responsiveness, need of a second IVIG dose, delay of treatment >10th day of illness, ages <1 year old and >8 years old, and the presence of sterile pyuria, aseptic meningitis, abdominal pain, and uveitis at diagnosis were found to have higher risk of coronary aneurysms (p < 0.05). Contrast to us, some researches outside of tropical region showed the lower percentage in coronary artery abnormalities. Cimaz reported only 2.2% of patients experienced with coronary artery aneurysm. Other coronary artery abnormalities were coded in 1.44% of patients, pericardial involvement in 1.48% of patients, myocardial involvement in 1.03%, cardiac valve disease in 0.5%, while 0.24% of patients had other cardiac complications [15]. Similarly, Saudankar showed 16.7% coronary artery ectasia/dilatation and 6.8% coronary artery aneurysms [16].

The efficacy of IVIG administered in the acute phase of KD is well established to reduce the prevalence of coronary artery lesion with higher doses given in a single infusion having the greatest efficacy [7], [22]. In our study, treatment with IVIG was given to 91.7% of the patients, in which, we have 35.1% of patients with late treatment, being in these cases more likely the development of aneurysms.

This retrospective study may have some limitations. It did not show the prevalence of KD in Hue Central Hospital due to lacking of epidemiology data. The number of subjects in this study was small, these data may not be representative of the current situation in Vietnam.

**Conclusion**

KD was very common in children under 5 years old with the high rate of coronary artery lesion. In the absence of a specific diagnostic test, the diagnosis of KD is mainly based on clinical criteria. Treatment with IVIG on or before 10 days of fever resulted in better coronary outcomes and decreased the total length of time of clinical symptoms.

**References**

1. Kawasaki T, Naoe S. History of Kawasaki disease. Clin Exp Nephrol. 2014;18(2):301-4. https://doi.org/10.1007/s10157-013-0877-6
2. Lin MT, Wu MH. The global epidemiology of Kawasaki disease: Review and future perspectives. Glob Cardiol Sci Pract. 2017;2017(3):e201720. PMid:29564341
3. Advani N, Sastroamoro S, Ontoseno T, Uiterwaal CS. Long-term outcome of coronary artery dilatation in Kawasaki disease. Ann Pediatr Cardiol. 2018;11(2):125-9. https://doi.org/10.4103/apc.apc_172_16
4. Viet PH. Clinical features, laboratory investigation and cardiovascular abnormalities in children with Kawasaki disease. Vietnam Med J. 2019;7(3):125-9.
5. Cox JR, Sallis RE. Recognition of Kawasaki disease. Perm J. 2009;13(1):57-61. PMid:21373247
6. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American heart association. Circulation. 2017;135(17):e927-e999. https://doi.org/10.1161/cir.0000000000000484
7. Gundoğdu F, Arslan S, Buyukkaya E, Senocak H. Treatment of a coronary artery aneurysm by use of a covered stent graft a case report. Int J Angiol. 2007;16(1):31-2. https://doi.org/10.1055/s-0031-1278242
8. Sakulchit T, Benseler SM, Goldman RD. Acetylsalicylic acid for children with Kawasaki disease. Can Fam Physician. 2017;63(8):607-9. PMid:28807964
9. Lang B. Recognizing Kawasaki disease. Paediatr Child Health. 2001;6(9):638-43. PMid:20084135
10. Lin YT, Manlhiot C, Ching JC, Han RK, Nield LE, Dillenburg R, et al. Repeated systematic surveillance of Kawasaki disease
in Ontario from 1995 to 2006. Pediatr Int. 2010;52(5):699-706. https://doi.org/10.1111/j.1442-200x.2010.03092.x
PMid:20113416

13. Singh-Grewal D, Wong M, Isaacs D. Diagnosis, treatment and outcome of Kawasaki disease in an Australian tertiary setting: A review of three years experience. J Paediatr Child Health. 2005;41(9-10):495-9. https://doi.org/10.1111/j.1440-1754.2005.00690.x
PMid:16150066

14. Sánchez-Manubens J, Antón J, Bou R, Iglesias E, Calzada-Hernandez J, Kawasaki Disease in Catalonia Working Group. Incidence, epidemiology and clinical features of Kawasaki disease in Catalonia, Spain. Clin Exp Rheumatol. 2016;34(3 Suppl 97):S139-44. https://doi.org/10.1186/1546-0096-12-s1-p123
PMid:26939753

15. Cimaz R, Fanti E, Mauro A, Voller F, Rusconi F. Epidemiology of Kawasaki disease in Italy: Surveillance from national hospitalization records. Eur J Pediatr. 2017;176(8):1061-5. https://doi.org/10.1007/s00431-017-2947-3
PMid:28612175

16. Saundankar J, Yim D, Itoh B, Payne R, Maslin K, Jape G, et al. The epidemiology and clinical features of Kawasaki disease in Australia. Pediatrics. 2014;133(4):e1009-14. https://doi.org/10.1542/peds.2013-2936
PMid:24685950

17. Chen JJ, Ma XJ, Liu F, Yan WL, Huang MR, Huang M, et al. Epidemiologic Features of Kawasaki Disease in Shanghai From 2008 Through 2012. Pediatr Infect Dis J. 2016;35(1):7-12. PMid:26372452

18. Son MB, Newburger JW. Kawasaki disease. Pediatr Rev. 2018;39(2):78-90. PMid:29437127

19. Abe J. Immunological aspects of Kawasaki disease. Nihon Rinsho. 2008;66(2):267-71. PMid:18265455

20. Tremoulet AH, Jain S, Chandrasekar D, Sun X, Sato Y, Burns JC. Evolution of laboratory values in patients with Kawasaki disease. Pediatr Infect Dis J. 2011;30(12):1022-6. https://doi.org/10.1097/inf.0b013e31822d4f56 PMid:21817952

21. Fernandez-Cooke E, Barrios Tascón A, Sánchez-Manubens J, Antón J, Grasa Lozano CD, Aracil Santos J, et al. Epidemiological and clinical features of Kawasaki disease in Spain over 5 years and risk factors for aneurysm development. (2011-2016): KAWA-RACE study group. PLoS One. 2019;14(5):e0215665. https://doi.org/10.1371/journal.pone.0215665 PMid:31107862

22. Furusho K, Kamiya T, Nakano H, Kyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet. 1984;2(8411):1055-8. https://doi.org/10.1016/s0140-6736(84)91504-6 PMid:6209513 4; 2(8411): 1055-8.