Kawasaki disease in Turkish children: a single center experience with emphasis on intravenous immunoglobulin resistance and giant coronary aneurysms

Murat Muhtar Yılmazer¹, Rahmi Özdemir¹, Timur Meşe¹, Mehmet Küçük¹, Taliha Öner¹, İlíker Devrim², Nuri Bayram², Barış Güven¹, Vedide Tavlı¹

Departments of ¹Pediatric Cardiology and ²Pediatric Infectious Diseases, Dr. Behcet Uz Children’s Hospital, University of Health Sciences, Izmir, Turkey. E-mail: rahmiozdemir35@gmail.com

Received: 8th February 2018, Revised: 16th August 2018, Accepted: 7th May 2019

SUMMARY: Yılmazer MM, Özdemir R, Meşe T, Küçük M, Öner T, Devrim İ, Bayram N, Güven B, Tavlı V. Kawasaki disease in Turkish children: a single center experience with emphasis on intravenous immunoglobulin resistance and giant coronary aneurysms. Turk J Pediatr 2019; 61: 648-656.

Prompt diagnosis and the administration of intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery abnormalities (CAA) in Kawasaki Disease (KD). The resistance to treatment and development of the coronary sequelae remain the most important problems in KD. We aimed to determine the predicting factors of nonresponse to initial IVIG therapy and to analyze the cases who had giant coronary aneurysms. A total of 120 KD cases, including 61 children fulfilling the criteria for KD and 59 with incomplete KD were enrolled into this study. Demographic, laboratory, clinical, echocardiographic characteristics, and treatment regimens were reviewed, retrospectively. The median age of the patients was 33.5 months (range: 3-168 months). Coronary artery aneurysms were detected in 35 patients (29%) at the time of diagnosis. Twenty-eight patients had coronary aneurysms small or medium in size, one had a large, and seven had giant coronary aneurysms. CAA persisted in 8 cases in the follow-up, all of which were large or giant aneurysms. A ten month-old girl with a giant coronary aneurysm was referred to coronary bypass surgery in the subacute phase of follow-up, due to myocardial ischemia. Eighteen patients were unresponsive to the initial IVIG therapy (%15), of whom 10 were diagnosed as cKD and 8 were iKD. Patients who did not respond to initial IVIG therapy, had higher white blood cell (WBC) count, higher C-reactive protein (CRP) and lower albumin levels than those who did (P<0.05). In univariate analysis; CRP, WBC and albumin were found to be significant predictors of nonresponse to initial IVIG therapy, while a stepwise multiple linear regression analysis showed that WBC count and albumin levels were significantly correlated with nonresponse to initial treatment with IVIG. Our study showed that WBC count and albumin levels might be used as predictors of nonresponse to the IVIG therapy in Turkish children with KD.

Key words: Kawasaki disease, giant coronary aneurysm, hypoalbuminemia, white blood cell count, intravenous immunoglobulin, treatment resistance.

Kawasaki disease (KD) is systemic inflammatory vasculitis of medium-sized muscular arteries, that occurs predominantly in infancy and early childhood.¹ KD is the most common cause of acquired heart diseases among children in developed countries. Coronary artery abnormalities (CAA) was reported to develop in 15% to 25% of untreated KD patients. Thus, KD may lead to myocardial infarction, sudden death, or ischemic heart disease.² Prompt diagnosis and the administration of intravenous
immunoglobulin (IVIG) can reduce the incidence of CAA from 25% to 4-5%. Approximately 85–95% of children treated with IVIG and acetylsalicylic acid respond promptly with resolution of inflammatory signs within 48 hours of treatment. However, about 11% to 23% of KD patients show an insufficient response to IVIG, which is characterized by persistent and recurrent fever 36 hours after the first IVIG infusion. Some studies suggested the association between nonresponse to IVIG treatment and certain laboratory parameters (low albumin level, high band count, high C-reactive protein (CRP), low hemoglobin level and high NT-pro Brain natriuretic peptide (BNP) level). Higher frequency of coronary artery lesions at admission has also been demonstrated in refractory patients. Although some scoring systems has been suggested, there have been no consensus on the factors predicting KD patients resistant to initial therapy. Another important issue regarding patients with KD is the development of giant coronary aneurysms. The possibility of spontaneous regression of these aneurysms is too low and they may potentially cause coronary stenoses and even myocardial infarction. Giant coronary aneurysms have been reported to be low in countries like Japan where the frequency of KD is high, while the incidence of giant aneurysms has been relatively higher in countries where the KD is less common. The aim of our study was to analyze the pediatric patients with KD, to determine the predicting factors of nonresponse to standard therapy and to analyze the patients who had giant coronary aneurysms.

Material and Methods

All children diagnosed with KD at Dr. Behçet Uz Children's Hospital, a paediatric tertiary referral hospital serving the entire Aegean region of Turkey, between June 2004 and June 2015, were included in the study. Data regarding demographic, laboratory, clinical, echocardiographic characteristics, and outcome of the patients were reviewed, retrospectively.

The diagnosis of Kawasaki disease was made by clinical symptoms such as; fever for 5 days or more, bilateral nonpurulent conjunctivitis, changes in oral mucosa and lips, exanthema along the trunk, changes in peripheral extremities and subsequent desquamation of finger tips, and cervical lymphadenopathy. Complete KD (cKD) was defined when fever for ≥5 days and at least 4 of the 5 principal criteria according to the previously published criteria were present. Incomplete KD (iKD) was defined when less than four classic clinical symptoms with supplemental laboratory criteria, regardless of coronary artery lesions, could be detected. Supplemental laboratory findings that support the diagnosis of iKD included the serum albumin level less than 3.0 g/dL, anemia for age, elevation of serum alanine aminotransferase level, platelet count ≥450 000/mm³, white blood cell count ≥15 000/mm³, and ≥10 white blood cells/high-power field in urinalyses.

Echocardiographic assessment of coronary abnormalities

Coronary artery abnormalities (CAA) including dilatation and aneurysm were assessed according to published criteria¹ using 2-dimensional echocardiography (Vivid-3 and Vivid S6, GE-Vingmed Ultrasound AS, Horten, Norway). Echocardiography was performed on admission, within one week of onset of illness, on second week, and subsequently repeated depending on the initial coronary lesions. Cardiac abnormalities other than coronary lesions were also evaluated.

Previously, we evaluated coronary arteries by means of the internal lumen diameter. We measured from the inner edges of coronary arteries and excluded points of branching. If the diameter of the internal lumen was ≥3 mm in children <5 years old, or ≥4 mm in children ≥5 years old, it was considered as pathologic.¹¹ Recently, Z-scores have been applied in the evaluation of coronary arteries. Therefore, we re-evaluated all coronary artery measurements using Z score for the standardization of all measurements. According to the last guideline No involvement: Z score always <2. Dilation only: Z score 2 to <2.5; or if initially <2, a decrease of ≥1 in Z score during follow-up.
Small aneurysm: Z score ≥2.5 to <5. Medium aneurysm: Z score ≥5 to <10, and absolute dimension <8 mm. Large or giant aneurysm Z score ≥10, or absolute dimension ≥ 8 mm.

**Treatment**

All patients were treated with 2 gr/kg of intravenous immunoglobulin G (IVIG) and high-dose aspirin 80 to 100 mg/kg/day during the acute phase of illness. After the fever subsided, low-dose aspirin 3 to 5 mg/kg/day were prescribed. Low dose aspirin was continued until detection of no evidence of coronary abnormalities by 6 to 8 weeks after the onset of disease. Nonresponse to IVIG therapy defined as persistent or recrudescent fever ≥36 hours after the completion of the initial IVIG infusion.\textsuperscript{1,11-13} Treatment with IVIG had been repeated (2 g/kg) in patients who failed to respond to initial IVIG infusion. We also used corticosteroid in patients who failed to respond to the subsequent dose of IVIG. Immunosuppressive or anti-TNF agents were selected in patients who did not respond to corticosteroids. The treatment algorithm currently used in our clinic is presented in Figure 1. Prevention of thrombosis in KD patients with CAA is one of the most important and therapeutic dilemma Although there is no prospective data guiding to choose an optimal anticoagulation regimen, last American Heart Association (AHA) guideline offers some plausible recommendations.\textsuperscript{1} We treated our patients in the manner recommended by the guidelines of the AHA published in 2004.\textsuperscript{11} If patients did not have CAA on echocardiography at any stage of the illness or patients with transient coronary artery dilatation, only low dose acetylsalicylic (ASA) was given the initial 6 to 8 weeks after the onset of illness. If patients had isolated (solitary) small to medium coronary aneurysm, long-term antiplatelet therapy with ASA was administered, until the aneurysm regressed. If patients had large coronary artery aneurysms or giant aneurysms, we administered a long-term therapy with low-dose aspirin together with warfarin to maintain an international normalized ratio (INR) of 2.0 to 2.5.

**Follow-up**

The patients diagnosed with KD were hospitalized until the fever subsided and acute phase reactants decreased to normal levels. All patients were evaluated for cardiac evaluation including Electrocardiography (ECG) and echocardiography one week after discharge. We examined the patients with persisting medium size coronary aneurysm at first, third and sixth month of admission, and then followed with six months’ intervals. Patients with coronary abnormalities that improved were revisited at first month and at sixth month after onset, and then annually followed-up. We performed stress tests every 1 to 3 years if the patient had medium aneurysm. Patients with large or giant coronary aneurysm were assessed every month up to 1 year of follow-up. Stress tests for induced myocardial ischemia including stress echocardiography or stress nuclear

---

**Fig. 1.** Treatment strategy of Kawasaki Disease currently used in our center.

IVIG: Intravenous immunoglobulin
ASA: Asetilsalisilik asit
TNF-\(\alpha\): Tumor necrosis factor alpha
medicine perfusion imaging was performed at least every 12 months or if the patient had symptoms. Anticoagulation treatment was continued as described above.

**Statistical analysis**

The statistical analysis was performed using the Statistical Package for Social Sciences version 17.0 (SPSS Inc, Chicago, IL, USA). Quantitative variables were analysed using the Kolmogorov-Smirnov test to assess sample normality. Student’s t-test was applied for normal samples, while the Mann-Whitney U test was used for inter-group comparisons of independent variables. Chi-square analysis was used for comparison of categorical variables, and associations between parameters were assessed using Pearson or Spearman’s correlation test. A p value <0.05 was considered statistically significant. The logistic regression test was used for determining the cause and effect relationship with the explanatory variables in binary and multiple categories of the categorical response variable. Hosmer-Lemeshow was used to assess goodness of fit for the logistic regression model. Stepwise multivariate linear regression model, including significant variables in univariate analyses, was then used to determine which determinants independently explained a significant (P<0.05) fraction of the variance of the dependent variables.

**Results**

A total of 120 KD cases including sixty-one children fulfilling the criteria for cKD and 59 with iKD were enrolled in this study. Demographic and laboratory data are presented in Table I. In the study group, 38% of the patients were under 2 years old, and 13% of the patients were under 1 year of age. There was no statistically significant difference between patients with cKD and patients with iKD in terms of the number of patients below 2 years of age (p>0.05). The most common clinical feature other than fever was red lips (%85), followed by bilateral non-purulent conjunctivitis (%70). The frequency of other clinical findings were cervical lymphadenopathy (69%), rash (64%), and extremity changes (41%). The median disease duration before diagnosis was 7 days (ranging from 5 to 18 days). Twelve patients had trivial mitral regurgitation at initial echocardiogram. CAA were detected in 35 patients (%29) at the time of diagnosis. Twenty-eight patients had coronary aneurysms small or medium in size, one had a large, and seven had giant coronary aneurysms. Coronary artery abnormalities had persisted in 8 cases in the follow-up including 7 giant and 1 large size aneurysms. Two giant aneurysms did not respond to standard treatment. Full regression of aneurysm size was not achieved in none of the giant aneurysms, whereas one patient showed a partial response. One patient underwent a coronary artery by-pass surgery in the acute stage. Incidence of giant coronary aneurysms under two years of age was higher when compared to children above 2 years of age. Moreover, median age of children with giant coronary artery aneurysms was significantly lower (median 16 months, ranging from 3 months to 12 years) when compared to the

| Table I. Summary of Demographic and Laboratory Data Before Initial Intravenous Immunoglobulin (IVIG) Therapy. |
| Age at onset (month) | 33.5 (3-168) |
| Gender (male/female) | 75/45 |
| Complete/incomplete cases | 61/59 |
| Duration of fever, days | 7 (5-18) |
| ESR, mm/h | 83.08±29.9 |
| CRP mg/dl | 8.96±6.4 |
| WBC, 103/mm³ | 15.04±6.8 |
| Hemoglobin, g/dl | 10.45±1.3 |
| Hematocrit level, % | 31.57±3.98 |
| Platelet count, 103/mm³ | 508.25±214.2 |
| ALT (IU/L) | 32 (9-721) |
| AST (IU/L) | 34.5(12-833) |
| Albumin g/dl | 2.96±0.6 |
| Sterile pyuria | 15 patiens (%12.5) |
| CAA on admission | 35 patients (%29) |

ESR: erytrocite sedimentation rate, WBC: white blood cell, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CAA: coronary artery abnormality.

Median values were given for age at onset, duration of fever, ALT, AST. Mean values±SD were given for ESR, CRP, WBC, hematocrit, hemoglobin, albumin.
The median age of children without giant coronary aneurysm (median 36 months, ranging from 6 months to 14 years), \( p=0.046 \).

**Non-responsive KD cases**

Non-response to initial IVIG therapy was present in 18 patients (\%15), of whom 10 were diagnosed as cKD and 8 were iKD. Second dose of IVIG was administered to all cases who did not recover with the initial IVIG therapy. Pulse methyl-prednisolone was administered to 8 patients who did not respond to second dose of IVIG. The clinical course of two of the patients who were resistant to steroid was worth mentioning. First case was a 2-year-old boy diagnosed as complete KD in 2007. He had giant aneurysms in left anterior descending artery (LAD) and right coronary artery (RCA), and his fever did not recover with IVIG and steroid therapy. Low dose methotrexate and anticoagulant therapy (warfarin) were commenced on the seventh day of his admission to the hospital. Although, his fever recovered rapidly, giant aneurysms did not regress. The other patient was a 10-month-old girl with the diagnosis of complete KD. Her echocardiogram revealed giant aneurysms located at LAD and RCA. Fever persisted more than eight days despite the treatment with IVIG and steroid. Her fever had recovered with parenteral anti-TNF (infliximab) treatment. However, a thrombus developed in a giant aneurysm located in the LAD with ischemic findings on ECG. Because of a rapid deterioration of left ventricular systolic functions, the patient was referred to another center for coronary bypass surgery. She had acceptable systolic functions on her follow-up after surgery. The treatment summary of our patients is presented in Figure 2.

Table II summarizes the comparison of the demographic, laboratory and clinical data between responders and non-responders to initial IVIG therapy. No significant difference was present between complete and incomplete cases in terms of nonresponse to IVIG therapy. Patients who did not respond to initial IVIG therapy had higher WBC count and CRP values than those in the responder group. The non-responder group also had lower albumin levels, 2.49 g/dL versus 3.06 g/dL, respectively \( (P<0.001) \). In univariate analysis; CRP, WBC and albumin were found to be significant predictors of nonresponse to initial IVIG therapy, while a stepwise multiple linear regression analysis showed that WBC count and albumin levels were significantly correlated with nonresponse to initial treatment with IVIG. The results of multivariate analysis are presented in Table III. There was no significant correlation between IVIG nonresponse and classical clinical findings of KD or CAA on initial echocardiogram in logistic regression analysis.

**Follow-up and anticoagulation**

Of the 35 patients (29%) with coronary artery involvement at the onset of disease, coronary sequelae remained in 8 patients (6.7%). Of which 7 had giant coronary aneurysms. We did not observe death or recurrent disease during the follow-up. All patients in this study had normal systolic functions except one patient who referred for coronary surgery. Coronary artery diameters in children with small or medium size aneurysms returned to

![Fig. 2. Treatment summary of Kawasaki Disease in our center.](image-url)
Table II. Demographic, Clinical and Laboratory Data Comparing Responders and Nonresponders Before Initial Therapy.

|                                | Responders | Non-responders | P value |
|--------------------------------|------------|----------------|---------|
| Number of cases                | 102        | 18             |         |
| Age at onset (month)           | 33 (3-40)  | 35.5 (9-168)   | 0.56    |
| Gender (male/female)           | 64/38      | 11/7           | 0.55    |
| Complete/incomplete cases      | 51/51      | 10/8           | 0.80    |
| Duration of fever (days)       | 7 (5-18)   | 7 (5-17)       | 0.64    |
| CAA on admission(n)            | 27         | 8              | 0.10    |
| Giant coronary aneurysm(n)     | 5          | 2              | 0.28    |
| Conjunctivitis, n (%)          | 72 (%71)   | 12 (%67)       | 0.78    |
| Oropharyngeal changes n (%)    | 81 (%79)   | 13 (%72)       | 0.54    |
| Rash n (%)                     | 62 (%61)   | 15 (%83)       | 0.054   |
| Lymphadenopathy n (%)          | 71 (%70)   | 12 (%67)       | 0.79    |
| Extremity changes n (%)        | 41 (%41)   | 8 (%44)        | 0.80    |
| ESR, mm/h                      | 81.61±29.1 | 91.22±33.8     | 0.21    |
| CRP mg/dl                      | 8.33±6.0   | 12.5±7.5       | 0.010   |
| WBC, 10³/mm³                   | 14.40±5.5  | 18.57±11.2     | 0.016   |
| Hemoglobin, g/dl               | 10.40±1.3  | 10.7±1.6       | 0.37    |
| Hematocrit level, %            | 31.48±3.7  | 32.04±5.2      | 0.58    |
| Platelet count, 10³/mm³        | 505.56±212.4 | 523.22±229.4   | 0.75    |
| AST (IU/L)                     | 35.5 (13-833) | 33.5 (12-150) | 0.23    |
| ALT (IU/L)                     | 32.0 (10-721) | 41 (9-181)    | 0.57    |
| Albumin g/dl                   | 3.06±0.6   | 2.49±0.7       | 0.00    |

ESR: erythrocyte sedimentation rate, WBC: white blood cell, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CAA: coronary artery abnormality.

Median values were given for age at onset, duration of fever, ALT, AST. Mean values±SD were given for ESR, CRP, WBC, hematocrit, hemoglobin, albumin.

Table III. A Stepwise Multivariate Linear Regression Analysis of Variables Influencing Unresponsiveness to IVIG Therapy.

| Variables     | β   | %95 confidence interval | P value |
|---------------|-----|-------------------------|---------|
| Albumin       | -0.248 | -0.256 to -0.036          | 0.010 |
| WBC count     | 0.020 | 0.001 to 0.017                   | 0.033 |
| CRP           | 0.133 | -0.003 to 0.018            | 0.155 |

R²: 0.161  
CRP C-reactive protein, WBC White blood cell count

Normal during the follow-up in all. We also discontinued the low dose ASA therapy 6-8 weeks in patients with no coronary involvement or dilatation only or aneurysm disappeared in the follow-up. Low dose ASA was continued in the patients with small or middle-sized coronary aneurysms on the follow-up while warfarin was also added to ASA therapy for the patients with giant coronary aneurysms.
Discussion

A marked decrease in the rate of coronary aneurysms with the use of IVIG has been reported in patients with KD. Nonresponse to standard IVIG treatment is one of the most important current problems in children with KD. Various studies showed that the incidence of nonresponse to IVIG treatment in children with KD was 10-20%. In our study, 18 patients (15%) did not respond to standard initial IVIG treatment. Our first study reported in 2010, involving 20 complete KD cases, demonstrated a treatment resistance rate of 25%. Wallace et al. and Ashouri et al. reported that the incidence of nonresponse to IVIG was 23% and 20%, respectively. There are also studies reporting a nonresponse incidence as low as 7.8%. Some studies suggested the association between nonresponse to IVIG treatment and certain laboratory parameters (low albumin level, high band count and low hemoglobin level). Our study showed that an elevated WBC count and a low albumin level before initial IVIG therapy were independent predictors of non-response to initial therapy. Hypoalbuminemia has been suggested to have a closer relationship with vascular leakage and complicates the process. Terai et al. suggested that vascular leakage may be a key feature of KD pathophysiology and vascular endothelial growth factor (VEGF) might play a role in the vascular leakage in KD. Albumin has the lowest molecular weight among plasma proteins. It can easily leave the vessels during inflammation, resulting in hypoalbuminemia. A low albumin level has also been used as a risk factor for choosing KD patients who will receive IVIG therapy in Japan. Ashouri et al. also observed that low albumin levels were associated with non-response to IVIG therapy. In addition, they reported that elevated band count and abnormal initial echocardiogram were also related to refractory cases and a more complicated clinical course. Similarly, to Ashouri et al., Do et al. also reported that low albumin, low sodium, and high neutrophil proportion were significantly present in the refractory cases. In our study, a univariate analysis showed that high CRP levels and WBC count were associated with nonresponse to initial IVIG therapy. However, only high WBC count and hypoalbuminemia were significant predictors of nonresponse in multivariate analysis. Xie et al. also reported that WBC count and albumin level may be used as effective predictors for IVIG resistance. Since, nonresponse to therapy is characterized by prolonged fever which represents an ongoing inflammatory process, inflammatory markers such as CRP and WBC count are expected to increase. Additionally, some authors mentioned a defect in inhibition of immunologic stimuli which caused an insufficient response to IVIG therapy. Therefore these patients may need a longer or more potent anti-inflammatory treatment. Some centers have used the scoring system suggested by Kobayashi et al. which claims to predict risk factors for IVIG-resistant cases. High serum levels of AST, CRP and high percentage of neutrophils, low age, low serum levels of sodium, low platelet counts and administration of IVIG early in the course of illness were used to detect refractory cases in this scoring system. Shin et al. and Do et al. also showed the usefulness and value of this scoring system in predicting refractory cases among Korean children. Davies et al. found the sensitivity and specificity of Kobayashi scoring system to be 58% and 35%, respectively in the British population. These results indicate that this scoring system could be effectively used in the Japanese and Korean populations but may not work in other populations.

We emphasized the high frequency of giant aneurysms in our study, as they might lead to severe complications. Giant coronary aneurysm has been reported to occur in approximately 0.2% of patients in Japan. In our study, we detected a giant coronary aneurysm in 7 patients (5.8%). Lyskina et al. reported a frequency of giant aneurysms of 5.7% in their Russian population. Ben Chehida also reported a giant aneurysm rate of 15% in a small Tunisian population. Increased awareness of the physicians in the diagnosis of KD and the immediate treatment before the development of exaggerated immune response in Japan could be the reasons why our study group had higher rate of giant aneurysms. Additionally, many mild cases which were never diagnosed might cause false impression that severe cases are higher than normal. Although five of seven
patients with giant aneurysms were under 2 years in our study, no significant difference between patients under and above two years of age was detected. We also did not find any significant effect of fever duration at the time of diagnosis of giant coronary aneurysm. Nevertheless, two complicated patients in our study had giant coronary aneurysms. Both of these patients had IVIG and steroid resistance, one of which received methotrexate and the other received infliximab. Thrombosis developed within the coronary aneurysm of the patient who received infliximab. Since, thrombus did not dissolve with anticoagulant therapy and ischemic findings developed, this patient was transferred for coronary bypass surgery. In our follow up, none of the giant aneurysms regressed, but mid-term follow-up results were uncomplicated. Giant aneurysms of coronary arteries are predisposed to coronary thrombosis and stenosis. Therefore, careful monitoring of patients for prevention of coronary thrombosis, and timely surgical intervention are recommended especially within the first 2 years.9,25

Retrospective design was the main limitation of this study. Several risk factors previously attributed to nonresponse to the therapy could not be investigated due to lack of laboratory and clinical parameters. The number of IVIG-nonresponders was relatively small to represent the sample.

Nerveless this study showed that WBC count and albumin, can be used as a predictor for unresponsiveness to therapy in Turkish children with KD. These results may be helpful for the management of KD patients and careful monitoring with echocardiogram. Further prospective randomized studies are needed to confirm the risk factors of nonresponse to IVIG. In our study, all patients with small to medium coronary artery aneurysms showed regression but none of the patients who had giant coronary aneurysm showed complete regression of the coronary lesions. Giant coronary aneurysms may show persistent dilatation, development of thrombi in an aneurysm or development of stenosis over time. Hence, careful monitoring and effective anticoagulation is needed.

REFERENCES

1. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation 2017; 135: e927-e999.

2. Kim DS. Kawasaki disease. Yonsei Med J 2006; 47: 759-772.

3. Ogata S, Tremoulet AH, Sato Y, et al. Coronary artery outcomes among children with Kawasaki disease in the United States and Japan. Int J Cardiol 2013; 168: 3825-3828.

4. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991; 324: 1633-1639.

5. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. Pediatrics 2000; 105: E78.

6. Xie T, Wang Y, Fu S, et al. Predictors for intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. Pediatr Rheumatol Online J 2017; 15: 17.

7. Ashouri N, Takahashi M, Dorey F, Mason W. Risk factors for nonresponse to therapy in Kawasaki disease. J Pediatr 2008; 153: 365-368.

8. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006; 113: 2606-2612.

9. Fukazawa R, Kobayashi T, Mikami M, et al. Nationwide survey of patients with giant coronary aneurysm secondary to Kawasaki disease 1999-2010 in Japan. Circ J 2018; 82: 239-246.

10. Lyskina GA, Bokeriya OL, Shirinskaya OG, et al. Giant aneurisms of coronary arteries in the Kawasaki syndrome. Kardiologiia 2017; 57: 76-84.

11. Newburger JW, Takahashi M, Gerber MA, et al; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004; 114: 1708-1733.
12. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr 2008; 153: 117-121.

13. Newburger JW, Sleeper LA, McCrindle BW, et al; Pediatric Heart Network Investigators. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med 2007; 356: 663-675.

14. Do YS, Kim KW, Chun JK, Cha BH, Namgoong MK, Lee HY. Predicting factors for refractory kawasaki disease. Korean Circ J 2010; 40: 239-242.

15. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Prachuabmoh C, Kangkagate C. Immunoglobulin failure and retreatment in Kawasaki disease. Pediatr Cardiol 2003; 24: 145-148.

16. Tavli V, Yilmazer MM, Gıven B, Meşe T, Oner T, Demirpençe S. Kawasaki hastalığında standart yüksek doz intravenöz gamoglobulin tedavisine yanıtlı olma riski. Türk Kardiyoloji Derneği Arşivi 2010; 38: 20-24.

17. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. Pediatr Infect Dis J 1998; 17: 1144-1148.

18. Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, Kohno Y. Prognostic impact of vascular leakage in acute Kawasaki disease. Circulation 2003; 108: 325-330.

19. Nakano M. Predictive factors of coronary aneurysm in Kawasaki disease correlation between coronary arterial lesions and serum albumin, cholinesterase activity, prealbumin, retinol-binding protein and immature neutrophils. Prog Clin Biol Res 1987; 250: 535-537.

20. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. Acta Paediatr Jpn 1991; 33: 805-810.

21. Matsubara T, Ichiyama T, Furukawa S. Immunological profile of peripheral blood lymphocytes and monocytes/macrophages in Kawasaki disease. Clin Exp Immunol 2005; 141: 381-387.

22. Shin J, Lee H, Eun L. Verification current risk scores for Kawasaki disease in Korean children. J Korean Med Sci 2017; 32: 1991-1996.

23. Davies S, Sutton N, Blackstock S, et al. Predicting IVIG resistance in UK Kawasaki disease. Arch Dis Child 2015; 100: 366-368.

24. Ben Chehida A, Ben Messaoud S, Ben Abdelaziz R, et al. High frequency of cardiovascular complications in Tunisian Kawasaki disease patients: need for a further awareness. J Trop Pediatr 2019; 65: 217-223.

25. Suda K, Iemura M, Nishiono H, et al. Long-term prognosis of patients with Kawasaki disease complicated by giant coronary aneurysms: a single-institution experience. Circulation 2011; 123: 1836-1842.