Evaluation of unresponsiveness to standard high-dose gamma globulin therapy in Kawasaki disease

Kawasaki hastalığında standart yüksek doz intravenöz gama globulin tedavisine yanıtsızlığın değerlendirilmesi

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Objectives: We investigated the incidence of unresponsiveness to intravenous gamma globulin (IVIG) treatment in Kawasaki disease (KD) and evaluated its relation with coronary artery involvement.

Study design: The study included 20 children (13 boys, 7 girls; mean age 4.2±3.4 years; range 9 months to 12 years) with KD. The mean disease duration on admission was 7.3±2.4 days (range 5 to 14 days). Initial treatment consisted of a single dose of IVIG and high-dose of aspirin. Unresponsiveness was defined as the persistence of fever and other symptoms within the first 48 hours of treatment. All the patients were evaluated by two-dimensional echocardiography before and after treatment. The mean follow-up period was 16.5±2.8 months (range 9 to 24 months).

Results: Unresponsiveness was seen in five patients (25%), who received a subsequent dose of IVIG, which improved fever in two patients. The remaining three patients received high-dose methylprednisolone. One patient who showed no response to either IVIG or methylprednisolone was treated with low-dose oral methotrexate. Six patients (30%) had coronary artery involvement (4 dilatations, 2 aneurysms), five patients on admission echocardiography, and one patient on control echocardiography seven days after treatment. Of five unresponsive patients, four (80%) had coronary artery involvement on admission. Patients with coronary involvement underwent coronary angiography after a mean of one year. Five patients had normal coronary arteries, whereas no angiographic regression was observed in one patient who had a giant coronary artery aneurysm on admission and was treated with oral methotrexate.

Conclusion: The incidence of unresponsiveness to treatment was markedly high in KD patients who had coronary artery involvement on admission.

Key words: Child; coronary disease; echocardiography; immunoglobulins, intravenous/therapeutic use; mucocutaneous lymph node syndrome/drug therapy; treatment failure.

Amaç: Bu çalışmada, Kawasaki hastalığı (KH) tanısıkonan olgularda uygulanan standart intravenöz gama globulin (İVİG) tedavisine yanıtsızlık oranı araştırıldı ve bunun koroner arter tutulumu ile ilişkisi değerlendirildi.

Çalışma planı: Çalışmaya, KH tanısıyla tedavi edilen 20 hasta (13 erkek, 7 kız; ort. yaş 4.2±3.4; dağılım 9 ay-12 yıl) alındı. Başvuru anındaki hastalık süresi ortalama 7.3±2.4 gün (dağılım 5-14 gün) idi. Hastalar başvuru anında tek doz İVİG ve yüksek doz aspirin ile tedavi edildi. Bu tedavi ile 48 saat içinde ateşin veya diğer semptomların gerilememesi tedaviye yanıtsızlık olarak değerlendirildi. Tüm olgular tedavi öncesi ve sonrasında ikiboyutlu ekokardiyografi ile değerlendirildi. Ortalama takip süresi 16.5±2.8 ay (dağılım 9-24 ay) idi.

Bulgular: Tedaviye yanıtsızlık beş hastada (%25) görüldü. Bu hastalara ikinci doz İVİG uygulandı. Bu tedaviyle ateş iki hastada gerileme gösterdi; üç hastaya ise yüksek doz metilprednizolon verildi. Hem iki doz İVİG tedavisine hem de metilprednizolona yanıt alınamayan bir hastaya düşük doz oral metotreksat verildi. Beş hastada başvuru anındaki ekokardiyografide, bir hastada tedavinin yedinci gününde olmak üzere toplam altı hastada (%30) koroner arter tutulumu (4 genişleme, 2 anevrizma) saptandı.

Tedaviye yanıt alınamayan beş hastanın dördünde (%80) başvuru sırasında koroner arter tutulumu vardı. Koroner arter tutulumu saptanan hastalara ortalama bir yıl sonra koroner anjiyografi yapıldı; beş hastada koroner arterler normal bulunurken, başvuru anında sol ana koroner arterde dev anevrizma saptanan ve oral metotreksat uygulanan hastada anevrizmanın devam ettiği görüldü.

Sonuç: Çalışmamızda başvuru anında koroner arter tutulumu olan KH'li olgularda tedaviye yanıtsızlık oranı belirgin olarak daha yüksek bulundu.

Anahtar sözcükler: Çocuk; koroner arter hastalığı;ekokardiyografi; immünglobulin, intravenöz/terapötik kullanım; mukokütan lenf nodu sendromu/ilaç tedavisi; tedavi başarısızlığı.

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Kawasaki disease (KD) is an acute febrile vasculitis of childhood characterized by coronary artery involvement. It is the most common cause of acquired pediatric heart diseases in many developed countries.[1,2] Although its etiology is not well understood, clinical and epidemiologic data point to an infectious trigger and a genetic susceptibility.[1,3] No specific test has been developed since the disease was first described in 1967.[4] Instead, certain criteria consisting of clinical findings are being used to arrive at a diagnosis. A fever of >5 days and the presence of at least four of the following are sufficient for the diagnosis of KD: bilateral non-exudative conjunctivitis, erythema of mucosa of the lips and mouth, extremity changes, eruptions, and cervical lymphadenopathy.[1] Coronary artery involvement (coronary artery aneurysm or dilatation) leading to long term ischemic disease and death is reported in 15-25% of untreated patients with KD.[1,5-7] Intravenous immunoglobulin (IVIG) and high-dose aspirin administered within the first 10 days of the disease has been reported to decrease the rate of coronary artery involvement from 20% to 5%.[1,8,9] Regression of fever and the other symptom within 48 hours of the onset of standard treatment demonstrates a response to treatment. On the other hand, persistence or recurrence of fever or the other symptom 48 hours after the onset of standard treatment indicates unresponsiveness or resistance to treatment. Unresponsiveness to treatment is one of the most current problems encountered in cases of KD.[1,8,10,11] Reports from various studies indicate that the incidence of resistance to IVIG treatment in patients with KD is 10-20%.[8,10-13]

In this study we investigated the incidence of unresponsiveness to the baseline standard IVIG treatment in patients diagnosed with KD and evaluated its relationship with coronary artery involvement during the follow-up period.

PATIENTS AND METHOD

A total of 20 patients (13 boys and 7 girls; mean age 4.2±3.4; range 9 months-12 years) who were hospitalized and receiving treatment at the Department of Pediatric Cardiology between March 2004 and June 2008, following the diagnosis of KD were included in the study. The mean disease duration on admission was 7.3±2.4 days (range 5 to 14 days). All patients had a fever lasting for ≥5 days, together with at least four of the five diagnostic criteria.[1] *(i)* bilateral non-exudative conjunctivitis; *(ii)* erythema of mucosa of the lips and mouth; *(iii)* extremity changes (erythema, indurations, desquamations, etc.); *(iv)* skin eruptions (also in the perineal region), and *(v)* unilateral cervical lymphadenopathy of >1.5 cm in diameter.

Patients with a fever of <5 days duration or those of had less than four of the five diagnostic criteria or patients whose diagnosis was made by echocardiographic findings and who did not satisfy the classical Kawasaki criteria were described as having atypical (incomplete) KD and excluded from the study. Demographic, clinical, echocardiographic, angiographic, and therapeutic data were obtained retrospectively from medical records. The disease duration and information about first-day fever were also obtained from records and the first day of fever was considered as the first day of the disease.

The standard method of diagnosing coronary artery involvement in patients with KD is by two-dimensional echocardiography (2D Echo) and is adequate in most patients. On the other hand, coronary angiography is recommended in these patients on an average of 6 months to one year after diagnosis. However, angiography is also recommended immediately after the acute phase of the disease in patients with any suspicion of a small aneurysm or in complex lesions requiring visualization of the coronary anatomy.[1,14] The first echocardiographic investigation was performed at the time of hospitalization and was repeated on the 3-7 days of treatment. Identification of coronary involvement by 2D Echo investigation was performed according to previously published criteria as follows:[1,15] *(i)* Lumen diameter of at least 3 mm for <5 years, of at least 4 mm for ≤5 years, or *(ii)* the inner diameter of a segment being at least 1.5-fold that of the neighboring segment, or *(iii)* presence of irregularities in the lumen. In addition, a lumen size of more than 8 mm in the unaffected area of the coronary artery was referred to as a giant aneurysm. All patients were re-evaluated by 2D Echo 10 days after discharge. The second follow-up evaluations were performed with one month, and later every 3-6 months. The mean follow-up duration was 16.5±2.8 months (range 9 to 24 months). Coronary angiography was performed after a mean period of one year of the diagnosis of coronary involvement.

On admission treatment of patients diagnosed with KD consisted of a single dose infusion of 2 g/kg of IVIG for 10-12 hours and high-dose (80-100 mg/kg/day) of aspirin divided into 4 doses. Aspirin was administered at anti-inflammatory dose (80-100 mg/kg/day) for at least 14 days. The dose was then reduced to 5 mg/kg/day and maintained for a period of two weeks. Anticoagulant therapy was initiated and maintained for an approximate follow up period of 14 days in one patient with a giant aneurysm whose coronary artery aneurysm could not regress with treatment during the follow-up.

Lack of improvement in the fever or the other symptoms within 48 hours of initiating standard IVIG treatment, or a recurrence of fever was described as unresponsiveness to treatment. Theses patients were

Table 1. Incidence of clinical symptoms of Kawasaki disease

	Mean±SD	Number	Percentage
Age (years)	4.2±3.4		
Gender			
Male		13	65
Female		7	35
Disease duration on admission (days)	7.3±2.4		
Follow-up period (months)	16.5±2.8		
Coronary artery involvement			
On admission		5	25
Follow-up period		6	30
Dilatation		4	20
Aneurysm		2	10
Unresponsiveness to intravenous immunoglobulin		5	25
Clinical findings			
Eruptions		18	90
Lips and mouth findings		19	95
Extremity changes		18	90
Conjunctivitis		16	80
Cervical lymphadenopathy		13	65

re-administered the same dose of IVIG (2 mg/kg).[2,8,12] On the other hand, high dose methylprednisolone (as a 2-3 hours infusion of 30 mg/kg) was administered to patients who were unresponsive to the second IVIG dose. A low dose (10 mg/m2) of oral methotrexate was administered to a patient who did not respond to this treatment approaches.[16]

RESULTS

Demographic and clinical findings of the patients and the distribution of clinical findings of Kawasaki disease are shown in Table 1. 75% of the patients were less than 5 years old. The boy-girl ratio was 2.1:1. Coronary artery involvement was observed in five patients who underwent 2D Echo on admission demonstrated. Coronary artery dilatation was identified in one patient on the seventh day of treatment (Table 1).

Fever persisted in five patients (25%) 48 hours after initiation of treatment, despite administration of standard treatment (single dose infusion of 2 g/kg of IVIG and high-dose 80-100 mg/kg/day of aspirin) to all patients after diagnosis. A second IVIG dose was administered to these patients who were evaluated as unresponsive to treatment. The fever improved in only two of these patients who received this treatment; the other three patients were given high dose (30 mg/kg) methylprednisolone. One patient who was diagnoses on admission with giant coronary artery aneurysm by 2D Echo did not respond to both IVIG and methylprednisolone (Figure 1); this patient's fever was kept under control with low dose methotrexate. Coronary artery involvement was identified in four of the five patients who were unresponsive to standard IVIG treatment on admission.

Characteristics of patients with coronary artery involvement are shown in Table 2. 80% of the patients who were diagnosed as having coronary involvement were found to be resistant to standard treatment. Six of the patients who were diagnosed with coronary involvement by 2D Echo underwent coronary angiography after a mean period of one year. The coronary artery was found to be normal in five patients. However, aneurismal formation was found to persist in one patient who was diagnosed with a giant coronary aneurysm on admission and whose fever was kept under control following oral methotrexate administration. No dilatation or aneurysm was observed following the standard follow-up method by 2D Echo, in the other patients who were unresponsive to treatment.

The duration of starting treatment in three patients was 10 days or more after the onset of fever. There was coronary dilatation in one of these patients; IVIG and methylprednisolone were given as a combination in this patient and the coronary artery involvement was found to regress. No myocardial infarction or death was reported through out the follow-up period.

Table 2. Characteristics of patients with coronary artery involvement

Age	Duration of starting treatment (days)	Coronary artery involvement on admission	Responsiveness status to treatment	Echocardiographic findings	Coronary artery involvement on angiography 1 year later
20	5	Present	Absent	Dilatation in RCA and LCA	Absent
2 years	9	Present	Present	Proximal LCA dilatation	Absent
2.5 years	10	Present	Absent	Giant aneurysm in LCA	Present
3.5 years	6	Present	Absent	Aneurysm in LCA	Absent
5.5 years	12	Present	Absent	RCA dilatation	Absent
12 years	7	Absent	Present	Proximal LCA dilatatioN	Absent

LCA: Left coronary artery; RCA: Right coronary artery

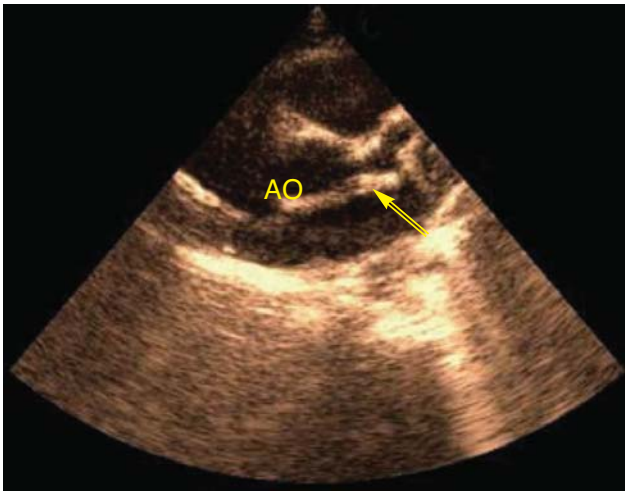

Figure 1. Two-dimensional echocardiography showing a giant aneurysm in the left main coronary artery

DISCUSSION

With the use of intravenous immunoglobulins, a marked decrease in the incidence of coronary involvement has been reported in patients with KD.[1] However, the mechanism of action of the effect of IVIG in the treatment of KD is not yet well understood. A great proportion of patients are currently known to be resistant to standard IVIG treatment of to be unresponsive to treatment. Approximately 10-20% of patients with Kawasaki disease are reported to be unresponsive to baseline IVIG treatment.[1,8,10-12,17] In our study, five patients (25%) were unresponsive to baseline IVIG treatment. The incidence of unresponsive to this treatment was reported to be 23% by Wallace et al.[12], and 20% by Ashouri et al.[10] On the other hand, there are studies which report an incidence of as low as 7.8%.[13] The high incidence rate of unresponsiveness in our study may be explained by the small sample size of our study and also due to the fact that most patients who were referred to our center were more severe cases, since most of the less severe cases preferred other centers. However, patients who were referred to our department were those who had not received baseline KD treatment at other centers. Some studies suggest the high incidence of unresponsiveness to be associated with some laboratory parameters (low albumin level, high band count and low hemoglobin level).[10,18,19] On the other hand, Ashouri et al.[10] demonstrated a significantly higher incidence rate in patients who were diagnosed with coronary artery involvement on admission. We also demonstrated that four of the five patients (80%) with coronary artery involvement on admission were unresponsive to IVIG treatment and their fever persisted 48 hours after treatment. On the other hand, resistance to baseline IVIG treatment was reported in one patient with coronary artery involvement, on the seventh day of presentation. Despite the limited number of patients in our study, the high incidence rate of unresponsiveness in patients with coronary artery involvement on admission, correlates with results of the study by Ashouri et al.[10] Some studies attribute the persistent fever to severity of the vasculitis and suggest that this is a strong predictor for the development of coronary artery aneurysm.[1,18,20] The incidence of coronary artery involvement was found to be markedly higher in patients who were unresponsive to IVIG treatment (those with persistent fever) (4/5, 80%), compared to those who were responsive (2/15, 13.3%). On the other hand, the reason for persistence of inflammation in patients with persistent fever despite IVIG treatment is not yet understood.[1] Coronary artery involvement is suggested to be directly related with the lower peak serum IgG level in some patients and that the duration of inflammation in these patients may prolong.[1] Consequently, anti-inflammatory treatment in patients unresponsive to treatment should be administered intensively in order to keep the inflammatory under control. Apart from one patient, regression of coronary artery involvement was reported following anti-inflammatory treatment in all the patients who were unresponsive to treatment.

The coronary artery is known to be affected in 15-25% of Kawasaki disease patients who are left untreated.[1,8,11,14] Administration of IVIG within the first 10 days of the disease has been reported to reduce the risk of coronary artery involvement from 20% to below 5%.[1,11] The incidence of coronary artery involvement in our study was found to be 30% (6/20 patients). This rate is slightly higher than the rate reported by literature studies (15-25%). There was coronary artery involvement in five of the 17 patients who received IVIG treatment within the first 10 days; which was reported to regress during the follow-up period, except in one patient with sever involvement. Coronary artery involvement was also reported in one of the three patients who initiated treatment 10 days or more after the onset of fever. There was regression of coronary artery involvement in this patient despite unresponsiveness to standard treatment. Results of this study show that regression of coronary artery involvement was not observed in one patient alone (5%) following treatment of six patients (30%) who had coronary artery involvement at baseline.

The retrospective nature of our study, the small sample size, and the inability to include atypical KD patients in the study were considered as limitations of our study.

In conclusion, KD continues to be the most common cause of acquired pediatric heart disease especially in developed countries. KD is currently known to be resistant to standard treatment. In this study, resistance to standard IVIG treatment in patients who had coronary artery involvement on admission was found to be signi-

ficantly higher than in those without coronary artery involvement. On the other hand, evaluation of follow-up results demonstrates that there was complete regression in all patients who responded to IVIG treatment, whereas coronary artery involvement was found to persist in one patient who was unresponsive to IVIG treatment.

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