Kawasaki Disease: More Patients Are Being Diagnosed Who Do Not Meet American Heart Association Criteria

Mark T. Witt, MD; L. LuAnn Minich, MD; John F. Bohnsack, MD; and Paul C. Young, MD

ABSTRACT. *Objective.* **To determine the frequency of Kawasaki disease (KD) diagnosis in patients who did and did not meet American Heart Association (AHA) diagnostic criteria and to examine the clinical findings, the time to treatment, and the outcomes of the two groups.**

Design. **Retrospective review of all patients with a discharge diagnosis of KD at a tertiary care children's hospital (1991–1997).**

Results. **A total of 127 patients were identified. All received intravenous immune globulin (IVIG) and had complete echocardiographic studies. AHA criteria were met in 81 (63.8%). More patients who did not meet criteria (9 of 46, 20%) had coronary artery abnormalities (CAA), compared with those who had the complete clinical picture (6 of 81, 7%). The 15 patients with CAA received IVIG later (12.4 ± 7.4 days) from onset of symptoms compared with those with no CAA (8.2 ± 4.6). The time period was the same for patients with CAA who met the criteria, (11.8 ± 5.8 days) as for patients who did not meet AHA criteria (12.8 ± 8.6 days). Infants were more likely than were older children to develop CAA, to receive IVIG later, and to be diagnosed with an incomplete clinical picture.**

Conclusion. **Physicians are increasingly likely to diagnose KD in patients who do not meet complete AHA criteria. Despite the potential risks of overdiagnosis and overtreatment, this practice seems justified because the complete criteria are an insensitive indicator of having or developing CAA.** *Pediatrics* **1999;104(1). URL: http://www.pediatrics.org/cgi/content/full/104/1/e10;** ***Kawasaki disease, intravenous immune globulin, coronary artery abnormalities.***

ABBREVIATIONS. KD, Kawasaki disease; CAA, coronary artery abnormalities; IVIG, intravenous immune globulin; AHA, American Heart Association.

Kawasaki disease (KD) is an acute febrile illness of unknown etiology characterized by an acute generalized vasculitis.[1] Prompt diagnosis is critically important, because the incidence of coronary artery abnormalities (CAA) can be reduced from 20% to 25% to <5% by early treatment with intravenous immune globulin (IVIG).[2,3] Diagnosis is based on clinical criteria summarized by the American Heart Association (AHA) in 1993.[4] These include fever for 5 or more days, a polymorphous exanthem, nonpurulent conjunctivitis, changes in the lips or oral cavity, redness and edema with later desquamation of the extremities, and at least one cervical lymph node that is >1.5 cm in diameter. The diagnosis is made when the child has ≥5 days of fever, four of the other five findings, and no evidence of another disease with similar clinical features.[4]

Problems applying the criteria in clinical situations develop, because it is difficult to exclude other causes of the nonspecific signs and symptoms, and because children can develop the CAA characteristics of KD without fulfilling the full AHA criteria. Reports of these atypical cases have increased over the last several years.[4–7] When KD is diagnosed, a cascade of events is initiated. These events include hospitalization, consultation with subspecialists, echocardiography, treatment with IVIG and aspirin, and extended follow-up with a pediatric cardiologist.[4,8,9] Therefore, pediatricians face a difficult clinical dilemma when evaluating a child with features of KD. Failure to make the diagnosis in a child with KD results in the child not receiving a highly effective therapy. Conversely, diagnosing KD in a child with some other condition means that the child may not receive appropriate treatment for his or her actual illness and that the child may be subjected to unnecessary and costly diagnostic and therapeutic interventions that may have side effects.

The investigators observed that, in recent years, clinicians seemed increasingly to be diagnosing and treating KD in children who did not meet AHA criteria for typical or atypical KD. We reviewed the recent experience with KD at our institution to determine whether this observation was accurate. The specific hypotheses of this retrospective study were: 1) between 1991 and 1997 the proportion of patients diagnosed with KD who did not meet AHA criteria had increased; 2) children who did not meet criteria had received IVIG earlier in the course of their illness than did those who met criteria; and 3) fewer children who did not meet criteria would be found to have CAA. We compared the clinical and demographic features of children who developed CAA with the features of those children who did not develop CAA, and we compared the findings in infants with the findings in older children.

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METHODS

The study was conducted at Primary Children's Medical Center, a 232-bed children's hospital in Salt Lake City, Utah that is the principal referral center for children living in the Intermountain West. After approval by the Primary Children's Medical Center's Research and Human Subjects Committee, we reviewed the records of all patients discharged with a diagnosis of KD between January 1, 1991 and December 31, 1997. Using a standardized form, we recorded the duration of fever, the presence of the other AHA criteria, the interval from earliest recorded findings of any of the criteria of treatment with IVIG, the presence of CAA determined by echocardiography, and the results of all laboratory tests that had been obtained. All patients had completed two dimensional and Doppler echocardiographic examinations using standard techniques with sedation as necessary. CAA were defined as ectasia of the coronary arteries compared with age-specific standards or the presence of saccular, fusiform, or giant aneurysms.[4] Categorical variables were compared using Fisher's exact test or the χ^2 statistic. Continuous variables were compared using the Student's t test or Mann Whitney U test if they were not distributed normally. $P < .05$ was set as the level of significance. Statistics were performed using Statview (Abacus Concepts, Inc, Berkeley, CA).

RESULTS

Proportion of Cases Meeting AHA Criteria Versus Not Meeting AHA Criteria Over Time

During the 7-year study period, 127 patients were diagnosed with KD. All patients received IVIG in a dose of 2 g/kg of body weight. Of the children, 81 (64%) met AHA criteria, and 46 (36%) did not. The number of patients who did and did not meet criteria for each year of the study are shown in Fig 1. The number of children who met criteria was relatively constant at ~12 per year with a range of 8 to 14, but there was an increase in the proportion of cases who did not meet criteria during the latter half of the study period. During 1995–1997, significantly more (45% of 67) patients did not meet AHA criteria compared with 1991–1994 (27% of 60 patients) (Fig 2). These data support our hypothesis that more cases in recent years were being diagnosed that did not meet AHA criteria.

Demographics, Clinical Features, and Outcomes of Children Who Did Meet Criteria Versus Children Who Did Not Meet Criteria

The demographic, clinical, and laboratory features of patients who met criteria and who did not meet AHA criteria are shown in Table 1. Although the mean ages of the two groups did not differ significantly, infants who were 12 months or younger were significantly more likely to be diagnosed as having KD without meeting complete criteria (see below and Table 4). There were no differences in the duration of fever or the presence of rash between the two groups, but, as would be expected, a higher percentage of the children who met criteria had the other findings. As noted by others, the least common finding in both groups was cervical adenopathy. Laboratory findings were similar. Patients who did not meet criteria did not receive IVIG sooner which suggests that they were not being diagnosed or treated earlier in the course of their illness than those who did meet the criteria. In addition, significantly more patients who did not meet criteria developed CAA (20%) compared with those who did meet criteria (7%). These data do not support the hypotheses that diagnosis of KD with an incomplete clinical picture results in earlier treatment and a better outcome.

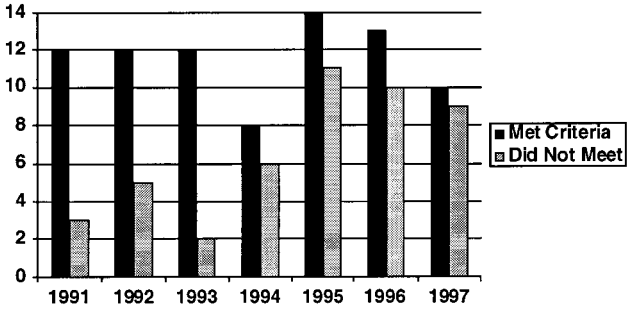

Fig 1. Diagnosis of KD by year of study.

Comparison of Patients With and Without CAA

CAA were found in 15 (11.8%) of the patients. The characteristics of patients with and without CAA are listed in Table 2. Although the mean ages of the groups did not differ significantly, infants who were 1 year or younger were significantly more likely to have CAA (see below and Table 4). Patients with CAA had significantly higher erythrocyte sedimentation rates and platelet counts and lower hematocrit levels suggesting a greater degree of inflammation.

Patients with CAA received IVIG ~4 days later and had fever ~2.5 days longer than did patients without CAA. Of the 15 patients with CAA, 2 had fever <5 days, whereas 8 had fever for >10 days before treatment. Of the 30 patients who received IVIG >10 days after onset of symptoms, 8 (27%) had CAA compared with 7 (7%) of the 97 patients who were treated ≤10 days ($P < .004$).

Of the 15 patients with CAA, 9 did not meet AHA criteria. Table 3 compares the clinical features of these children with the features of children who met criteria. Only the presence of extremity changes approached statistical significance, but, because of the small numbers, these findings should be interpreted with caution.

Comparison of Infants and Older Children

Characteristics of children younger and older than 1 year are presented in Table 4. Infants made up 13% (17 of 127) of the series but accounted for 8 (53%) of the 15 patients with CAA ($P < .0001$). Infants were more likely to be diagnosed without meeting criteria and more likely to receive IVIG later than were older children. The difference in time to treatment among the 8 infants with CAA (13.9 days) and the 7 without CAA (8.4 days) was not statistically significant, but this comparison also involves small numbers of patients. There was no difference in the likelihood of developing CAA when infants who met criteria were compared with infants who did not. Of the 17 infants, 10 did not meet AHA criteria; 5 (50%) of these developed CAA, compared with 3 (43%) of the 7 who did meet criteria.

DISCUSSION

The data demonstrate that in recent years practitioners in our institution have diagnosed KD in an

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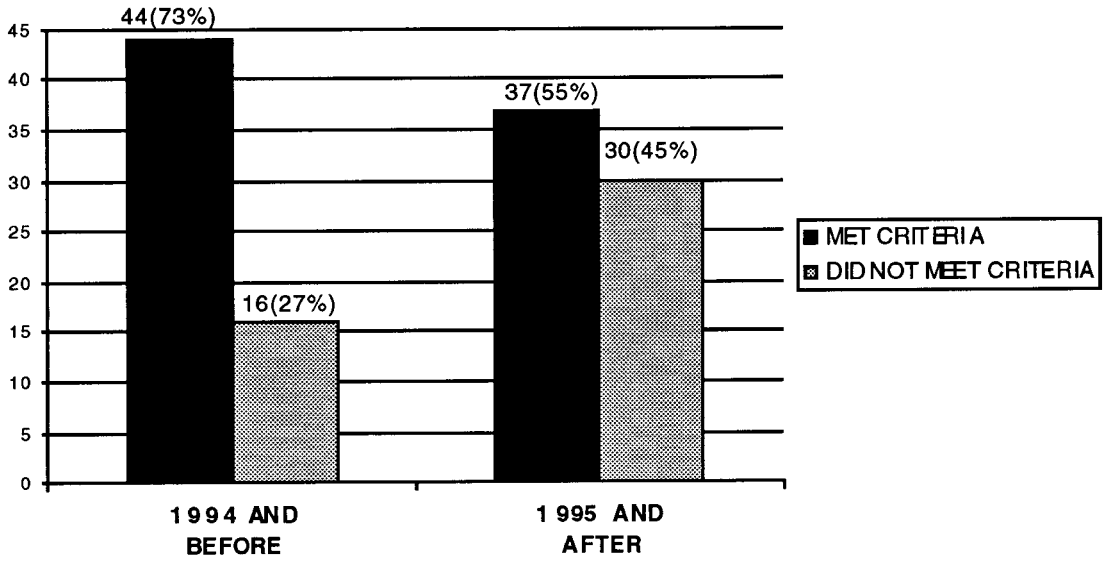

Fig 2. Diagnosis of KD: comparison of the first and second halves of the study. $P < .03$ (χ^2).

TABLE 1. Comparison of Patients Who Did and Did Not Meet Criteria

Characteristic	Met Criteria $n = 81$	Did Not Meet Criteria $n = 46$	Significance
Age (mo) (mean ± SD)	43.7 ± 31	39.6 ± 39	NS
% Female	44	33	NS
No. days of fever (mean ± SD)	7.9 ± 4.5	7.2 ± 4.1	NS
% With rash	100	96	$P = .058$*
% With oral mucosal changes	98	85	$P < .009$
% With conjunctivitis	96	78	$P < .002$*
% With extremity changes	85	48	$P < .001$*
% With cervical nodes	64	13	$P < .0001$*
WBC/mm^3	14 813	15 866	NS
ANC/mm^3	13 270	11 294	NS
Platelets × 1000/mm^3	431	449	NS
Hematocrit %	34.1	33.7	NS
ESR mm/h (mean ± SD)	79.9 ± 35	70.4 ± 35	NS
Treatment (mean ± SD)	8.6 ± 4.9	8.9 ± 5.7	NS
Number (%) with CAA	6 (7)	9 (20)	$P < .05$**

* χ^2 test; ** Fisher's exact test.

TABLE 2. Comparison of Patients With and Without CAA

Characteristic	CAA Present $N = 15$	CAA Absent $N = 112$	Significance
Age (mo; mean ± SD)	33 ± 48	43.4 ± 32	NS
% Female	40	40	NS
No. days of fever (mean ± SD)	9.9 ± 4.9	7.4 ± 4.3	$P = .034$*
% With rash	100	98	NS
% With conjunctivitis	93	89	NS
% With oral mucosal changes	80	95	NS
% With extremity changes	53	74	NS
% With cervical nodes	26	48	NS
WBC/mm^3	14 773	15 254	NS
ANC/mm^3	10 700	13 000	NS
Platelets × 1000/mm^3 ± SD	540 ± 173	425 ± 167	$P = .017$*
Hematocrit % (mean ± SD)	29 ± 5	35 ± 5	$P < .0001$*
ESR mm/h (mean ± SD)	102 ± 32	73 ± 34	$P = .003$*
Days to IVIG Rx (mean ± SD)	12.4 ± 7.4	8.2 ± 4.6	$P = .0029$*
# (%) Met AHA criteria	6 (40)	75 (67)	$P = .046$**

* Student's t test; ** χ^2 test.

increasing proportion of patients who do not meet AHA criteria. The most likely explanation for this practice is the reluctance of clinicians to withhold an effective therapy in children who might have KD and, therefore, could be at risk to develop CAA. The awareness of atypical KD, a condition defined by the presence of CAA in children who do fulfill the standard diagnostic criteria for KD, probably accounts for this behavior. Clinicians may perceive that patients who have some features of KD but who do not

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TABLE 3. Patients with CAA: Comparison of Clinical Features in Those Meeting and not Meeting Criteria

	Met Criteria $N = 6$	Did Not Meet Criteria $N = 9$	P Value
Days of fever (mean ± SD)	9.5 ± 3.3	10.2 ± 5.9	NS
Days to IVIG (mean ± SD)	11.8 ± 5.8	12.8 ± 8.5	NS
No. (%) with rash	6 (100)	9 (100)	NS
No. (%) with ext. changes	5 (83)	3 (33.3)	.057
No. (%) with conjunctivitis	6 (100)	8 (89)	NS
No. (%) with mucosal changes	6 (100)	6 (66.7)	NS
No. (%) with cervical adenopathy	3 (50)	1 (11)	NS

TABLE 4. Infants Under 1 Year Compared With Older Children

Characteristic	Infant $N = 17$	Child $N = 110$	Significance
% Female	59	37	NS
No. days of fever (mean ± SD)	9.2 ± 5.8	7.4 ± 4.1	NS
% With rash	100	98	NS
% With conjunctivitis	82	90	NS
% With oral mucosal changes	82	94	NS
% With extremity changes	71	72	NS
% With cervical nodes	29	48	NS
WBC/mm^3	16 405	15 000	NS
ANC/mm^3	14 200	12 300	NS
Platelets × 1000/mm^3 (mean ± SD)	540 ± 183	422 ± 164	$P = .0095$*
Hematocrit % (mean ± SD)	30.0 ± 5.6	34.6 ± 4.2	$P < .0001$*
ESR mm/h (mean ± SD)	82 ± 40	75 ± 34	NS
No. days to IVIG Rx (mean ± SD)	11 ± 7.6	8.4 ± 4.6	$P = .049$*
No. (%) met AHA criteria	7 (41)	74 (67)	$P = .037$**
No. (%) with CAA	8 (47)	7 (6.3)	$P < .0001$**

* Student's t test; ** χ^2 test.

meet all the criteria are at an earlier stage of their disease and that treating them at this stage before they develop the complete clinical picture will prevent them from developing CAA. In our series, CAA were more likely to be found in patients who did not meet AHA criteria. Of the 15 patients with CAA, 9 (20%) were from the 46 patients who did not meet criteria, whereas only 6 (7%) were from the 81 who did meet criteria. This difference was not accounted for by a longer interval between the onset of symptoms and IVIG treatment, and it was not associated with differences in laboratory findings.

The primary goal of recognizing and treating children with KD is to prevent CAA. The risk of developing CAA increases as the interval between onset of symptoms and administration of IVIG lengthens. Several studies and reviews have indicated that treatment is beneficial if received within the first 10 days.[3,4] Patients in our series who developed CAA received IVIG later in the course of their illness (12.4 vs 8.2 days), but 7 of the 15 patients who developed CAA received IVIG within 10 days of symptoms, suggesting that, in some patients with KD, CAA are present very early in the course of the illness. Physicians at our hospital administered IVIG to all patients as soon as the diagnosis was made, although this interval was sometimes >10 days. In 1 patient, IVIG was given after CAA were recognized. We were unable to find published evidence that treatment after 10 days is of value.

We found that infants younger than 1 year were more likely to be diagnosed without meeting criteria, to receive IVIG later, and to have CAA than were older children. Infants also had higher platelet counts and lower hematocrit levels. These findings are consistent with those of other reports.[10,11]

This study points out the need for better diagnostic tools to determine which children with features suggestive of KD are actually at risk to develop CAA. Although we found statistically significant differences among some of the features in children with and without CAA, the amount of overlap in the findings prevents them from being clinically useful for any individual patient. In our series, 36% of the patients did not meet criteria. However, they accounted for 60% of the patients with CAA. Therefore, the increasing tendency of clinicians to treat patients who have clinical findings suggestive of KD but who do not meet the full AHA criteria seems justified, although this practice almost certainly results in some children being labeled and managed as if they had KD, when they do not. Unnecessary treatment is not without consequences, because it is expensive, associated with potential side effects, and it may result in a perception of vulnerability, which is particularly likely when parents are told that their child's illness might affect his or her heart.[12,13]

This study is limited, because it is a retrospective chart review. Complete data were not available for every patient. In addition, a retrospective study has two types of ascertainment bias: 1) we not know what the outcome would have been for patients who did not meet the criteria if they had not been treated and 2) there may have been patients who actually had KD but who were given another diagnosis by their physician and thus did not come to our attention. Although a prospective study could address some of these problems, clinicians will continue to

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face a difficult dilemma until sensitive and specific diagnostic tests for KD are developed. This will require better understanding of the condition's etiology and pathogenesis.

CONCLUSION

The practice of diagnosing KD in children who do not meet AHA criteria has been increasing in recent years. This practice seems justified, because diagnosis based on the complete AHA criteria is an insensitive predictor of CAA. More patients with partial findings developed CAA than did those with the full clinical picture. Earlier treatment with IVIG was associated with a lower risk of developing CAA. Infants were more likely to have CAA and to present with an atypical clinical picture than were older children. More sensitive and specific diagnostic tests for KD are needed.

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