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Associated Symptoms in the Ten Days Prior to Diagnosis of Kawasaki disease

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Abstract

Objective—To describe common associated symptoms within the ten days prior to diagnosis in subjects enrolled in the Pediatric Heart Network's trial of steroid therapy in Kawasaki disease (KD).

Study design—Patients with acute KD were enrolled between days 4 and 10 of illness at 8 centers between 2002 and 2004. We defined common associated symptoms as those occurring in ≥ 10% of patients. Principal clinical criteria for KD were not included in this analysis.

Results—Among 198 patients, irritability was reported in 98 (50%), vomiting in 88 (44%), decreased food/fluid intake in 73 (37%), cough in 55 (28 %), diarrhea in 52 (26%), rhinorrhea in 37 (19%), weakness in 37 (19%), abdominal pain in 35 (18%), and joint pain (arthralgia or arthritis) in 29 (15%). One or more gastrointestinal symptom (vomiting, diarrhea, or abdominal pain) was present in 120 patients (61%) and 69 patients (35%) had ≥ 1 respiratory symptom (rhinorrhea or cough).

Conclusions—Nonspecific symptoms occur commonly in children with KD. To reduce delays in diagnosis, clinicians should be educated that such symptoms may comprise a significant component in the chief complaint.

Keywords

Kawasaki disease; febrile illness

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology.(1) First described in 1967 by Dr. Kawasaki in Japan,(2) KD is now a leading cause of acquired heart disease in children.(3) Without treatment, approximately one in five affected children will develop coronary artery aneurysms.(1,4) Conventional treatment with high-dose intravenous

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immunoglobulin (IVIG) and aspirin reduces the prevalence of coronary abnormalities approximately five fold.(5,6) Therapy should be administered within ten days, and ideally within seven days,(5,7) of fever onset.

Accurate and timely diagnosis of KD is challenging, however, because of the absence of a diagnostic test. Instead, clinicians must rely upon the presence of specific clinical criteria and laboratory data that support the diagnosis of KD, excluding other illnesses that could mimic the disease.(1) In addition to the cardinal manifestations of KD (i.e., fever, rash, bilateral nonexudative conjunctival injection, erythema of the lips and oral mucosa, changes in the extremities, and cervical lymphadenopathy), affected children often have associated symptoms that may delay diagnosis.(8) Few prospective data have been collected on their prevalence. The purpose of this report is to describe common symptoms, collected prospectively during the Pediatric Heart Network's multi-center randomized trial of steroid therapy in KD.(9)

Methods

Selection criteria and methods of the randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki are published elsewhere. (9) Patients were enrolled between Day 4 and 10 of illness from eight hospitals in North America between December 2002 and December 2004. Admission criteria included being on Day 4 –10 of illness (Day 1 was defined as the first day of fever) and having either a) ≥ 4 principal clinical criteria,(1) b) coronary artery z score(1) in the proximal right coronary artery (RCA) or left anterior descending coronary artery (LAD) ≥ 2.5 by two-dimensional (2-D) echocardiogram, together with two principal clinical criteria for patients under age six months and three principal clinical criteria for children ≥ age six months, or c) a coronary aneurysm by Japanese Ministry of Health criteria(10) plus at least one principal clinical criterion. We excluded children with prior treatment with IVIG; treatment with steroids, other than inhaled forms, in the prior two weeks; presence of another disease known to mimic Kawasaki disease; previous diagnosis of Kawasaki disease;(1) contraindication to steroid use; and inability to take aspirin. Patients were assigned to receive a single-dose of intravenous methylprednisolone (IVMP, 30 mg/kg of body weight over 2–3 hours) or placebo infusion, as well as conventional therapy with IVIG and aspirin.

Study nurses used a comprehensive code sheet including events, signs, and symptoms in their prospective completion of data forms (Appendix 2; available at www.jpeds.com). Instructions were reviewed at a central training session prior to study initiation, but the criteria for recording each potential clinical symptom or event (e.g., diarrhea, vomiting) were not standardized. Associated symptoms were obtained from parent interviews and observations of primary caregivers, coded and recorded at the following time points: 1) in the ten days prior to study enrollment (i.e., after diagnosis and before treatment); 2) during hospitalization, subsequent to enrollment; 3) from hospital discharge until the one week follow-up visit; and 4) from the one-week until the five-week visit.(9) Adverse events have been previously reported.(9) We analyzed all symptoms and report here those occurring in at least 10% of patients within the ten days prior to study enrollment, excluding principal clinical criteria.

Patient subgroups were classified according to the presence or absence of symptoms. We compared the distribution of continuous variables by patient subgroup using a t-test if normally distributed and Wilcoxon rank sum test otherwise. We used a Fisher exact test to compare the percentage of patients with a specific finding according to treatment group (i.e., placebo versus IVMP), sex and retreatment with IVIG for persistence of fever after initial therapy. Analysis of covariance, adjusting for age, was used to estimate the mean difference in laboratory values in patients with and without specific symptoms; the laboratory tests included hematocrit, white blood count (WBC), absolute neutrophil count, platelet count, erythrocyte sedimentation rate

(ESR), C-reactive protein (CRP), alanine aminotransferase (ALT), albumin, IgG, IgA, and IgM. All analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Of 199 subjects enrolled, one withdrew consent immediately after being randomized, so data were analyzed for 198 subjects. Study nurses recorded the occurrence of 93 types of associated symptoms, i.e., excluding the principal clinical criteria. Of these, nine symptoms occurred in more than 10% of study subjects in the ten days prior to diagnosis and form the basis of this report. Because none of the associated symptoms varied according to treatment assignment (e.g., IVMP versus placebo), our analyses are performed in the study cohort as a whole.

In the ten days prior to diagnosis, a history of irritability was noted in 98 (50%), vomiting in 88 (44%), decreased food/fluid intake in 73 (37%), cough in 55 (28%), diarrhea in 52 (26%), rhinorrhea in 37 (19%), weakness in 37 (19%), abdominal pain in 35 (18%), and joint pain (arthralgia or arthritis) in 29 (15%). When symptoms within ten days prior to diagnosis were grouped, 120 subjects (61%) had at least one gastrointestinal symptom and 69 (35%) had at least one respiratory symptom. The frequencies of symptoms from fever onset through completion of follow-up are described in Table I.

We explored whether symptoms within the ten days prior to diagnosis were associated with abnormalities in laboratory measures prior to treatment. In univariate analysis, absolute neutrophil counts were higher in subjects with joint pain ($p = .029$) and abdominal pain ($p = .019$), and tended to be higher among patients with vomiting ($p = .051$). Median ALT was higher in patients with vs. without vomiting (median, range: 47 [5 – 300] unit/L vs. 28 [5– 885] unit/L, $p = .028$) and with vs. without abdominal pain (median, range: 64 [13 – 325] unit/L vs. 28 unit/L [5 – 885], $p = .009$). Adjusting for age at enrollment, mean IgA was significantly lower in patients with diarrhea (age-adjusted mean, 82.0 ± 8.7 vs. 105.4 ± 5.7 g/L, $p = .026$). Patients with a cough had a higher ESR at diagnosis ($p = .017$). Although univariate analyses suggested associations of lower hematocrit and IgA with irritability, as well as lower IgA with abdominal pain, these associations were no longer significant after adjusting for age. Interestingly, the degree of inflammation, as indicated by ESR and CRP, was not significantly associated with irritability. A greater number of symptoms was significantly associated with later illness day at diagnosis in univariate analyses ($p = .005$), but this relationship was no longer significant ($p = .351$) in multivariate analysis adjusting for center and age.

We analyzed the relationship of patient age to reporting of the most common symptoms within ten days prior to diagnosis (Table II). Patients with irritability and rhinorrhea had a younger mean age than those without these symptoms ($p < .001$ and $p = .032$, respectively). Conversely, patients with symptoms of vomiting ($p = .009$), abdominal pain ($p < .001$), and arthralgia/joint pain ($p = .016$) were older than those without such symptoms. The overall prevalence of associated findings did not differ according to sex or day of illness at diagnosis. Patients with and without associated symptoms were similar with respect to the change in coronary dimensions from baseline to five weeks after randomization, expressed as z scores adjusted for body surface area.

Discussion

We found that nonspecific symptoms, such as vomiting, diarrhea, abdominal pain and cough, occur commonly in the ten days prior to diagnosis of KD. These nonspecific symptoms may reflect diffuse vasculitis or be the sequelae of an infectious trigger(s) of KD. Although less likely, we cannot exclude the possibility that associated symptoms result from concurrent infections unrelated to Kawasaki disease.(11)

Younger children were more likely to be described as irritable, whereas older children were able to report specific symptoms such as abdominal pain. Although associated symptoms do not contribute to the principal criteria for diagnosis and treatment of KD, it is important for clinicians to be aware that they may comprise a significant component in the chief complaint. Indeed, these symptoms may cause confusion with other common febrile illnesses and delay the diagnosis of KD.

Few previous reports quantify the prevalence of associated symptoms in KD. In a sub-study of an earlier prospective, multi-center trial of IVIG treatment in patients with KD, Burns et al reported on clinical and epidemiologic characteristics of patients referred for evaluation of possible KD.(12) However, their report focused on physical findings and laboratory data rather than on associated symptoms at the time of diagnosis. In an early single-center retrospective review, Hicks and Melish described their experience with KD in Honolulu.(13) Arthritis occurred in 30% of KD patients, of whom one-third had symptom onset in the first week of illness. The description of other associated symptoms was qualitative. In a subsequent review, these authors reported gastrointestinal complaints, including abdominal pain, diarrhea and nausea, in approximately one third of patients during the acute phase of the illness.(14) They also noted a high prevalence of irritability during the acute phase, consistent with our finding that at least half of KD patients were reported to be irritable in the ten days prior to diagnosis.

Our data should be viewed in light of their limitations. Although code sheets were designed to code all potential symptoms, criteria for coding symptoms were not standardized among study nurses at the beginning of the trial. Thus, nurses might have varied in their thresholds for coding specific symptoms. It is likely that the frequency of symptoms reported in this manuscript is a lower bound of the true incidence. Furthermore, coding of symptoms was based upon history obtained from parents as well as clinical observation by caregivers and is thus less precise and consistent than physical examination or laboratory data. Nonetheless, parental report and caregiver observation provides an important source of information for the practitioner considering the diagnosis of KD. We did not record the specific time within 10 days of illness that associated symptoms appeared and/or disappeared. Finally, testing for infectious diseases, such as viral serologies or cultures, were not mandated by protocol and were only done at the discretion of the primary caregivers.

In view of the absence of a diagnostic test or pathognomonic finding for KD, these data are useful in the evaluation of the febrile infant and child. Nonspecific symptoms that occur in many childhood febrile illnesses are common in children with KD, and their presence should not cause the clinician to discount the possibility of KD in patients with otherwise characteristic clinical and laboratory findings.(1)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Frequency of Symptoms over Time

Associated Findings and Events	At any Time During the Study Period	Within the 10 Days Prior to Diagnosis	During Hospitalization	Week 1 Follow-Up	Week 5 Follow-Up
			N(%)		
Number of Subjects	198	198	198	198	198
Irritability	118 (60)	98 (50)	30 (15)	35 (18)	12 (6)
Vomiting	104 (53)	88 (44)	12 (6)	16 (8)	4 (2)
Cough	77 (39)	55 (28)	13 (7)	17 (9)	17 (9)
Decreased food/fluid intake	76 (38)	73 (37)	12 (6)	9 (5)	6 (3)
Diarrhea	66 (33)	52 (26)	13 (7)	11 (6)	3 (2)
Rhinorrhea	63 (32)	37 (19)	6 (3)	15 (8)	23 (12)
Weakness	48 (24)	37 (19)	5 (3)	10 (5)	4 (2)
Abdominal pain	42 (21)	35 (18)	8 (4)	8 (4)	1 (1)
Joint pain	47 (24)	29 (15)	6 (3)	19 (10)	14 (7)
Diarrhea, vomiting or abdominal pain	140 (71)	120 (61)	31 (16)	30 (15)	8 (4)
Cough or rhinorrhea	99 (50)	69 (35)	16 (8)	22 (11)	30 (15)

TABLE 2

Age of Patients According to Symptoms within the 10 Days Prior to Diagnosis

Finding/Event	Present	Not Present	P Value
	Mean Age (yrs) ± S.D. (n)		
Irritability	2.7 ± 1.7 (98)	3.8 ± 2.5 (101)	**<.001**
Vomiting	3.7 ± 2.4 (88)	2.9 ± 2.0 (111)	**.009**
Cough	3.1 ± 2.6 (55)	3.3 ± 2.1 (144)	.627
Decreased food/fluid intake	3.4 ± 2.6 (73)	3.2 ± 2.0 (126)	.604
Diarrhea	3.1 ± 2.3 (52)	3.3 ± 2.2 (147)	.574
Rhinorrhea	2.6 ± 1.9 (37)	3.4 ± 2.3 (162)	**.032**
Weakness	3.8 ± 2.6 (37)	3.1 ± 2.2 (162)	.107
Abdominal pain	5.0 ± 2.0 (35)	2.9 ± 2.1 (164)	**<.001**
Arthralgia/Joint Pain	4.2 ± 2.1 (29)	3.1 ± 2.2 (169)	**.016**