

Associated Symptoms in the Ten Days Before Diagnosis of Kawasaki Disease

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Objective To describe common associated symptoms within the 10 days before 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 $\geq 10\%$ 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. (*J Pediatr* 2009;154:592-5)

Kawasaki disease (KD) is an acute systemic vasculitis of unknown cause.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 1 in 5 affected children will develop coronary artery aneurysms.^{1,4} Conventional treatment with high-dose intravenous immunoglobulin (IVIG) and aspirin reduces the prevalence of coronary artery abnormalities approximately 5-fold.^{5,6} Therapy should be administered within 10 days, and ideally within 7 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 on 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 (ie, 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 multicenter 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 8 hospitals in North America between

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*A list of additional Pediatric Heart Network Investigators available at www.jpeds.com (Appendix I).

Supported by National Institutes of Health grants U01 HL068285 and RR 02172 (J.N., A.B., R.P. Sundel); U01 HL068270 (M.L., G.K.), U01 HL068292 (L.M., L.L.), U01 HL068281 (A.A.), U01 HL068290 (R.K.), U01 HL068269 (J.L.), U01 HL068288 (E.R.), and U01 HL068279 (V.V.) from the National Institutes of Health, and by the Ciarnanello Family Fund (A.B., J.N.). The authors declare no conflicts of interest, real or perceived.

Registered with clinicaltrials.gov (no.) NCT00132080.

Submitted for publication May 27, 2008; last revision received Sep 4, 2008; accepted Oct 3, 2008.

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0022-3476/\$ - see front matter

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10.1016/j.jpeds.2008.10.006

ESR	Erythrocyte sedimentation rate	IVMP	Intravenous methylprednisolone
IVIG	Intravenous immunoglobulin	KD	Kawasaki disease

Table I. Frequency of symptoms over time

Associated findings and events	At any time during the study period	Within the 10 days before diagnosis	During hospitalization	Week 1 follow-up	Week 5 follow-up
No. of subjects	198	198	198	198	195
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%)

December 2002 and December 2004. Admission criteria included being on Day 4 to 10 of illness (Day 1 was defined as the first day of fever) and having either (1) ≥ 4 principal clinical criteria,¹ (2) coronary artery z score¹ in the proximal right coronary artery or left anterior descending coronary artery ≥ 2.5 by 2-dimensional (2-D) echocardiography, together with 2 principal clinical criteria for patients younger than age 6 months and 3 principal clinical criteria for children \geq age 6 months, or (3) a coronary artery aneurysm by Japanese Ministry of Health criteria¹⁰ plus at least 1 principal clinical criterion. We excluded children with prior treatment with IVIG; treatment with steroids, other than inhaled forms, in the prior 2 weeks; presence of another disease known to mimic Kawasaki disease; previous diagnosis of Kawasaki disease¹; 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 before study initiation, but the criteria for recording each potential clinical symptom or event (eg, 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 10 days before study enrollment (ie, after diagnosis and before treatment); (2) during hospitalization, subsequent to enrollment; (3) from hospital discharge until the 1-week follow-up visit; and (4) from the 1-week until the 5-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 10 days before 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 by use of 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 (ie, 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 cell count, absolute neutrophil count, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein, alanine aminotransferase, albumin, and immunoglobulin G, A, and M. All analyses were conducted with SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Of 199 subjects enrolled, 1 withdrew consent immediately after being randomized, so data were analyzed for 198 subjects. Study nurses recorded the occurrence of 93 types of associated symptoms, that is, excluding the principal clinical criteria. Of these, 9 symptoms occurred in more than 10% of study subjects in the 10 days before diagnosis and form the basis of this report. Because none of the associated symptoms varied according to treatment assignment (eg, IVMP versus placebo), our analyses are performed in the study cohort as a whole.

In the 10 days before 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 10 days before diagnosis were grouped, 120 subjects (61%) had at least 1 gastrointestinal symptom, and 69 (35%) had at least 1 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 10 days before diagnosis were associated with abnormalities in laboratory measures before treatment. In univariate analysis, absolute neutrophil counts were higher in subjects with joint

Table II. Age of patients (mean \pm SD [n]) according to symptoms within the 10 days before diagnosis

Finding/event	Present	Not present	P value
Irritability	2.7 \pm 1.7 (98)	3.8 \pm 2.5 (101)	<.001
Vomiting	3.7 \pm 2.4 (88)	2.9 \pm 2.0 (111)	.009
Cough	3.1 \pm 2.6 (55)	3.3 \pm 2.1 (144)	.627
Decreased food/ fluid intake	3.4 \pm 2.6 (73)	3.2 \pm 2.0 (126)	.604
Diarrhea	3.1 \pm 2.3 (52)	3.3 \pm 2.2 (147)	.574
Rhinorrhea	2.6 \pm 1.9 (37)	3.4 \pm 2.3 (162)	.032
Weakness	3.8 \pm 2.6 (37)	3.1 \pm 2.2 (162)	.107
Abdominal pain	5.0 \pm 2.0 (35)	2.9 \pm 2.1 (164)	<.001
Arthralgia/joint pain	4.2 \pm 2.1 (29)	3.1 \pm 2.2 (169)	.016

pain ($P = .029$) and abdominal pain ($P = .019$), and tended to be higher among patients with vomiting ($P = .051$). Median alanine aminotransferase was higher in patients with versus without vomiting (median, range: 47 [5-300] unit/L vs 28 [5-885] unit/L, $P = .028$) and with versus without abdominal pain (median, range: 64 [13-325] unit/L vs 28 unit/L [5-885], $P = .009$). Adjusting for age at enrollment, mean immunoglobulin A (IgA) was significantly lower in patients with diarrhea (age-adjusted mean, 82.0 \pm 8.7 vs 105.4 \pm 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 C-reactive protein, 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 10 days before 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 5 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 10 days before 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, multicenter trial of IVIG treatment in patients with KD, Burns et al¹² reported on clinical and epidemiologic characteristics of patients referred for evaluation of possible KD. 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 Melish¹³ described their experience with KD in Honolulu. Arthritis occurred in 30% of patients with KD, 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 patients with KD were reported to be irritable in the 10 days before 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 on 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 or disappeared. Finally, testing for infectious diseases, such as viral serologic studies or cultures, was not mandated by protocol and was 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

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APPENDIX I. PEDIATRIC HEART NETWORK INVESTIGATORS

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Appendix 2. Code List E

Code	Associated findings and events
Noncardiac diagnoses	
A-0001	Abdominal pain
A-0002	Acne
A-0003	Anaphylaxis
A-0004	Anemia (hematocrit < 30 mg/dL)
A-0005	Anterior uveitis (documented by ophthalmology examination)
A-0006	Arthralgia
A-0007	Arthritis, proximal interphalangeal joints
A-0008	Arthritis, distal interphalangeal joints
A-0009	Arthritis, ankles
A-0010	Arthritis, elbows
A-0011	Arthritis, hips
A-0012	Arthritis, knees
A-0013	Arthritis, shoulders
A-0014	Arthritis, wrists
A-0015	Aseptic meningitis (confirmed by lumbar puncture)
A-0016	Beau's lines
A-0017	Blurred vision
A-0018	Bulbar conjunctivitis
A-0019	Cervical lymphadenopathy (>1.5 cm)
A-0020	Complication of intravenous line
A-0021	Cough
A-0022	Cyanosis
A-0023	Death
A-0024	Desquamation, genitourinary area
A-0025	Desquamation, lips
A-0026	Diabetes insipidus
A-0027	Diarrhea
A-0028	Dyspnea
A-0029	Dysuria
A-0030	Elevated liver function test (>2 times normal)
A-0031	Encephalitis
A-0032	Erythema, palms
A-0033	Erythema, soles
A-0034	Eczema
A-0035	Fluid retention/edema
A-0036	Flushing
A-0037	Headache
A-0038	Hearing loss
A-0039	Hemolytic anemia
A-0040	Hives
A-0041	Hydrops of gall bladder (documented by ultrasound scanning)
A-0042	Hyperglycemia (glucose > 150 mg/dL)
A-0043	Hypertension (SBP > 95 th percentile)
A-0044	Hypotension (SBP < 5 th percentile)
A-0045	Increased appetite
A-0046	Insomnia
A-0047	Irritability
A-0048	Mood changes
A-0049	Nervousness
A-0050	Pancreatitis

Appendix 2. Continued

Code	Associated findings and events
A-0051	Periungual desquamation, hands
A-0052	Periungual desquamation, feet
A-0053	Pneumonia (documented by chest radiography)
A-0054	Pseudotumor cerebri
A-0055	Psoriasis
A-0056	Pustular psoriasis
A-0057	Rash, new onset
A-0058	Rash, hives
A-0059	Rash, eczema
A-0060	Rash, pustular psoriasis
A-0061	Renal failure (creatinine > 1.5 mg/dL)
A-0062	Rhinorrhea
A-0063	Rigors
A-0064	Sepsis, suspected (not confirmed)
A-0065	Sepsis (confirmed by blood cultures)
A-0066	Shock
A-0067	Seizures
A-0068	Small bowel obstruction
A-0069	Sterile pyuria
A-0070	Strawberry tongue
A-0071	Strep throat (confirmed by throat culture)
A-0072	Sudden increase in fever
A-0073	Torticollis
A-0074	Vomiting
A-0075	Weakness
A-9999	Other non-cardiac, specify
Cardiac diagnoses	
B-0001	Aneurysms (peripheral aneurysms)
B-0002	Angina
B-0003	Arrhythmia
B-0004	Cardiac arrest
B-0005	Cardiac catheterization
B-0006	Cardiogenic shock
B-0007	Chest pain, not likely to be cardiac
B-0008	Chest pain, cardiac related
B-0009	Congestive heart failure (CHF)
B-0010	Dizziness, complaints of
B-0011	Exercise intolerance (by history)
B-0012	Gallop
B-0013	Myocardial infarction (confirmed)
B-0014	Myocardial infarction (suspected)
B-0015	Myocardial ischemia (fixed defect)
B-0016	Myocardial ischemia (reversible defect)
B-0017	New-onset CHF, weight gain
B-0018	New-onset CHF, hepatomegaly
B-0019	New-onset CHF, pulmonary edema
B-0020	New-onset CHF, cardiac enlargement
B-0021	New-onset CHF, gallop
B-0022	Palpitations
B-0023	Syncope
B-0024	Tachycardia (sinus rhythm > 200 beats/min)
B-9999	Other cardiac, specify