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Delayed Diagnosis by Physicians Contributes to the Development of Coronary Artery Aneurysms in Children With Kawasaki Syndrome

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Abstract

Background—A diagnosis of Kawasaki syndrome is based on clinical criteria with nonspecific laboratory findings, and there is a substantial risk of coronary artery aneurysms if treatment with intravenous immunoglobulin is delayed. In this study, we examined the contributions of sociodemographic factors and parent and physician behavior to the development of coronary artery aneurysms in children with Kawasaki syndrome.

Methods—We performed a retrospective, case-control chart review of Kawasaki syndrome patients treated at our institution during an 11-year period (1991–2002). Of 324 patients, 21 patients had coronary artery aneurysms and were matched with 81 Kawasaki syndrome control patients without coronary artery aneurysms.

Results—Patients who developed coronary artery aneurysms were more likely to have had their diagnosis established after 10 days of fever as a result of a delay in physician recognition of Kawasaki syndrome. In addition, these patients were also more likely to have been hospitalized at an outside facility with an erroneous diagnosis, to have had a greater number of healthcare visits before diagnosis, to have sought medical care in Mexico, to lack medical insurance and to speak Spanish as a primary language. Independent predictors of delayed diagnosis included incomplete clinical signs of Kawasaki syndrome, seeking health care in Mexico, and being hospitalized at an outside facility with a different diagnosis.

Conclusions—Increased risk of coronary artery aneurysms is associated with a delay in diagnosis by physicians and not with a delay in seeking medical consultation by parents. Sociodemographic factors influence the likelihood that patients will have a delayed diagnosis.

Keywords

Kawasaki syndrome; vasculitis; coronary artery aneurysms; Hispanic patients; sociodemographic factors

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Despite the availability of an effective treatment of Kawasaki syndrome, children continue to develop preventable morbidity and mortality from complications of this acute vasculitis. Kawasaki syndrome resolves spontaneously, but coronary aneurysms occur in as many as 25% of untreated children.¹ Nonetheless, high-dose intravenous immunoglobulin (IVIG) administered within the first 10 days of fever significantly reduces the risk of coronary artery aneurysms (CAAs) by unknown mechanisms.² The cause of Kawasaki syndrome is unknown, and there is no specific laboratory test to identify affected children.³ As a result, Kawasaki syndrome presents a dilemma for the clinician: the disease has protean manifestations and can be difficult to recognize, the diagnosis is based only on clinical criteria with supportive laboratory studies and there is a substantial risk of serious cardiovascular damage or rarely death if the therapy is not administered early in the course of the illness. Thus, timely diagnosis of this condition is critical.

Many children develop CAA each year in our community, despite the best intentions of clinicians to recognize and treat these children promptly. In San Diego County, the average annual incidence of Kawasaki syndrome is 21.1 per 100,000 children less than 5 years of age, and approximately 50–70 new cases are diagnosed each year (Annie S. Kao, unpublished data). During the study period, 6.5% of Kawasaki syndrome patients developed CAA, which is consistent with a recent report from a different geographic area.⁵ Therefore, despite effective therapy, children continue to develop potentially preventable morbidity from Kawasaki syndrome for reasons that remain obscure.

A great deal of attention has been paid to restructuring the clinical guidelines for diagnosing Kawasaki syndrome,³ but little attention has been paid to the potential for sociodemographic factors and healthcare-seeking behaviors to impact the diagnosis and treatment of this syndrome. Although factors such as cultural differences in explanatory models of illness⁶ and socioeconomic differences in access to health services⁷ might account for delays by parents in seeking health care for children with symptoms of Kawasaki syndrome, they may also influence the ability of providers to diagnose and treat Kawasaki syndrome in a timely manner (eg, limitations in ability to obtain a good patient history, failure to recognize symptoms that have come and gone). In this study, we examined the contribution of delayed diagnosis by physicians, delayed consultation of physicians by parents and sociodemographic factors to disease outcome.

METHODS

Patients

We performed a retrospective case-control study using a complete database of 324 Kawasaki syndrome patients hospitalized and treated at Rady Children's Hospital San Diego or University of California San Diego Medical Center between June 1, 1991 and July 30, 2002. All study subjects met the revised American Heart Association criteria for Kawasaki syndrome diagnosis.³ CAAs were diagnosed by serial echocardiograms and were defined as focal dilatation of a coronary artery 1.5 times the internal diameter of an adjacent segment or with a z-score >3 standard deviations from the mean internal diameter normalized for body surface area.⁸ Of the 324 patients, 21 patients (6.5%) developed CAA by echocardiographic criteria. We selected as controls for each patient with CAA (CAA+) 4 Kawasaki syndrome patients without CAA (CAA-) whose date of fever onset was closest to the CAA+ case, with 2 controls preceding and 2 cases following the index case. Cases with CAA who were aged less than one year were matched with controls less than 1 year. Controls were used only once. All but 2 CAA+ patients were successfully matched (within 1 day to 2.4 years) with 4 CAA- patients. For 2 CAA+ patients who were infants and presented late in the study period, one patient had only 2 matched controls while the other patient had three. A total of 81 CAA- controls were used in the analysis.

Data Collection

Patients were identified by study number to protect confidentiality. This study was approved by the University of California San Diego and Rady Children's Hospital San Diego institutional review boards. Demographic information, including age, gender, self-declared ethnicity, self-declared primary language, number of siblings, birth order, zip code of residence and health insurance status were obtained from emergency department records, admission history and physical examination records, and consult notes. Median household income by census tract was estimated from data produced by the San Diego Association of Governments. These estimates, based on population and housing characteristics for small geographic areas, were controlled to the California Department of Finance January 1 jurisdictional-level household count. Health insurance status was divided into 3 categories for analysis: government assistance, private insurance and no insurance/self-pay. Patients with government assistance were defined as patients with MediCal, HMO-Medicaid or California Children's Services.

The features and timeline of clinical presentation were also obtained from the medical record. These data included illness day at onset of diagnostic signs as reported by the parent, types of healthcare settings used (physician office or clinic, urgent care, emergency department, healthcare facility in Mexico), number of visits to healthcare providers prior to diagnosis and hospitalization with an alternative diagnosis. Illness day 1 was defined as the first day of fever. Delayed diagnosis was defined as the diagnosis of Kawasaki syndrome by a healthcare provider after illness day 10. For each patient, the time from fever onset until diagnosis was divided into 2 components: the time between illness day 1 and the patient's first healthcare contact and the time from the first healthcare contact to the illness day at diagnosis.

Statistical Analyses

Differences in the sociodemographic characteristics and features of service utilization of CAA+ and CAA- patients and patients with and without a delayed diagnosis were assessed by means of χ^2 tests for categorical variables and Mann-Whitney tests and Spearman correlation coefficients for continuous or ordinal measures. In addition to age and sex, demographic characteristics and features of service utilization found to be statistically significant ($P < 0.05$) were entered into multiple logistic and linear regression models to assess independent predictors of CAA or delayed diagnosis. Two sets of logistic models were created, one set including specific healthcare facilities visited by the patient prior to obtaining a diagnosis of Kawasaki syndrome (model 1) and one set including a summary measure of 3 or more visits to any and all healthcare facilities prior to obtaining a diagnosis (model 2). Multiple linear regression models were created to identify independent predictors of the days to first physician consultation by a parent and the days taken by a physician to reach an accurate diagnosis. A 2-tailed 0.05 significance level was used for all parameters. Analyses were performed with SPSSPC, version 11.0.

RESULTS

Characteristics of Patients With and Without CAA

The sociodemographic characteristics and features of service utilization of CAA+ and CAA- patients are presented in Table 1. CAA+ patients had significantly more days of fever before diagnosis of Kawasaki syndrome (12.6 days vs. 7.1 days, $P < 0.001$). These patients had more visits to healthcare providers and were more likely to have been hospitalized and treated at another institution for a mistaken diagnosis before a correct diagnosis of Kawasaki syndrome. In addition, a greater proportion of CAA+ patients sought health care in Mexico and lived in households where Spanish was spoken as the primary language. There was no difference in the time to medical consultation by parents between the 2 groups. However, the CAA+ patients had a longer time before diagnosis by a physician ($P < 0.001$).

To assess the independent risk factors for development of CAA in patients with acute Kawasaki syndrome, all categorical variables found to be significantly ($P < 0.05$) associated with CAA (Spanish as a primary language, health insurance status, healthcare visits to Mexico, hospitalizations during illness and delayed diagnosis) were entered into a multiple logistic regression model (Table 2). Independent of other factors, CAA+ patients were almost 8 times ($P = 0.001$) more likely to have been diagnosed after illness day 10 (model 1). When different healthcare settings were combined in the analysis (model 2), patients with CAA were 7.1 times ($P = 0.001$) more likely to have had a delayed diagnosis but no more likely to have had 3 or more healthcare visits (OR 2.5, $P = 0.19$). Both models exhibited adequate goodness of fit (model 1: $\chi^2 = 25.78$, $df = 5$, $P < 0.0001$; model 2: $\chi^2 = 25.82$, $df = 4$, $P < 0.0001$) with both models correctly classifying 85.3% of study participants.

Characteristics of Patients With and Without a Delayed Diagnosis

To investigate potential factors that lead to delayed diagnosis, the study population was stratified into 2 groups: Kawasaki syndrome patients with and without delayed diagnosis. Of the 102 Kawasaki syndrome patients in our study population, 28 (27.5%) had a delayed diagnosis; and of these 28 patients, 14 (50%) had CAAs. The sociodemographic characteristics and features of service utilization of the groups with and without delayed diagnosis were compared (Table 3). Patients with a delayed diagnosis were significantly more likely to have had more total visits to a healthcare provider and to be missing 2 or more diagnostic signs at the time of diagnosis.

To examine independent predictors of delayed diagnosis, we entered the categorical variables shown in Table 4 to be significantly associated with delayed diagnosis (missing 2 or more diagnostic signs at diagnosis, hospitalization at another healthcare facility and 3 or more visits to any health care facility) into 2 multiple logistic regression models. Independent of other risk factors, patients with a delayed diagnosis were 7.5 times ($P = 0.024$) more likely to have been hospitalized at another healthcare facility for a mistaken diagnosis prior to obtaining a diagnosis of Kawasaki syndrome, and almost 3 times ($P = 0.032$) more likely to be missing 2 or more diagnostic signs than patients without a delayed diagnosis (model 1). When different types of health-care facilities were grouped (model 2), patients were almost 6 times ($P = 0.002$) more likely to have made 3 or more visits to a healthcare provider and 3 times ($P = 0.028$) more likely to be missing 2 or more of the diagnostic signs than patients without a delayed diagnosis. Both models exhibited adequate goodness of fit (model 1: $\chi^2 = 10.91$, $df = 2$, $P = 0.004$; model 2: $\chi^2 = 16.51$, $df = 2$, $P < 0.0001$) with model 1 and model 2 correctly classifying 75.5% and 78.4% of study participants, respectively.

Additional univariate and multivariate analyses were conducted to identify predictors of delayed diagnosis by physicians and delayed consultation of physicians by parents. Spanish-speaking parents sought health care earlier in the course of the illness than non-Spanish-speaking parents (2.4 ± 1.8 days vs. 3.3 ± 2.6 days, $P < 0.05$). There was no significant association between delayed consultation of physicians by parents and lack of health insurance (2.6 ± 0.8 days vs. 3.2 ± 0.3 days for parents without insurance). In contrast, delayed diagnosis by physicians was significantly associated with the number of visits to healthcare providers ($r = 0.43$, $P < 0.001$) and the number of missing clinical criteria for the Kawasaki syndrome case definition ($r = 0.24$, $P < 0.05$). Significantly longer delay in diagnosis by physicians was also experienced by patients living in households where Spanish was the primary language (6.9 ± 5.5 days vs. 4.7 ± 3.9 days, $P < 0.05$) or who had no health insurance (8.3 ± 6.7 days vs. 4.8 ± 3.9 days, $P < 0.05$). However, when controlling for potential confounders, none of the patient characteristics was independently associated with delayed consultation of physicians by parents, and the only significant independent predictors of delay in diagnosis by physicians

were the number of visits to a healthcare provider and presence of less than 4 clinical criteria (Table 5).

DISCUSSION

In this study, we examined sociodemographic factors that might influence the development of CAA as a sequela of the vasculitis associated with acute Kawasaki syndrome. We found that the only significant independent risk factor for CAA was delayed diagnosis. Delayed diagnosis was further examined as the sum of the number of days before medical consultation by parents and the number of days before physicians diagnosed Kawasaki syndrome. We found that the most important factor in delayed diagnosis was a delay by the physician, which in turn was associated with multiple visits to a healthcare provider for the same illness and incomplete clinical signs. Hospitalization at another facility with an erroneous diagnosis was an independent risk factor for delayed diagnosis.

The study was conducted in San Diego, a border community of approximately 3 million residents with a population that is 52% non-Hispanic white, 28% Hispanic white and 10% Asian (estimated from the 2000 U.S. census). Studies have documented that many Mexican-born, U.S. residents preferentially seek health care across the border in Mexico where they perceive that they can receive more culturally competent care.⁹ Other reasons to seek health care in Mexico may include lower cost for individuals without health insurance and the widespread practice of evening office hours, obviating the need for parents to miss work. In the univariate analysis, Spanish as a primary language, lack of health insurance and seeking health care in Mexico were all significantly associated with the group that developed CAA. Restricted access to health care due to lack of health insurance may account for the findings in previous studies that Kawasaki syndrome patients are more likely to come from middle and upper-middle class families.^{7,10,11} However, our data show that these characteristics are not associated with delay in seeking medical consultation by parents but rather are associated with delayed diagnosis by physicians.

Our data further show that Spanish-speaking parents bring their children in, on average, even earlier than others, and that recognition of Kawasaki syndrome by physicians who serve this population needs improvement. A practical solution might be to target education about Kawasaki syndrome diagnosis to these healthcare providers.

Limitations of this study include the small sample size, the use of hospital records as the primary source of information and the retrospective study design. Potential biases introduced by the retrospective collection of data include omissions in the physician histories, use of parent self-reported ethnicity and date of initial appearance of symptoms and inaccuracies in dates of physician encounters.

In a recent study by Anderson et al,⁵ which examined factors contributing to delayed diagnosis of Kawasaki syndrome, it was also noted that the time to first physician visit was similar between the groups diagnosed before or after day 10 of illness. This suggests that parents easily recognized the severity of their child's illness. With respect to the healthcare providers in the present study, recognition of Kawasaki syndrome was delayed in children who lacked one or more of the classic criteria. It should be emphasized that the clinical signs of Kawasaki syndrome are often not all present at any one point in time and the existence of a language barrier may have made accurate medical histories difficult to obtain. Thus, physicians may have missed important historical clues to the diagnosis due to communication failure. Appearance of the clinical signs of Kawasaki syndrome over a protracted period of time was also a risk factor for delayed diagnosis in the study by Anderson et al.⁵ Together, these studies suggest that resources should be directed toward healthcare provider education and adoption

of the new American Heart Association guidelines that specifically address the approach to the patient with incomplete diagnostic criteria.³

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TABLE 1

Characteristics of Patients With Acute Kawasaki Syndrome Stratified by Coronary Artery Status

Characteristic	With CAA (n = 21)	Without CAA (n = 81)	P
Age (mo) (median, range)	11.7, 1.8–44.5	11.8, 1.8–138.5	NS
Males (%)	66.7	61.7	NS
No siblings (%)	23.5	20.9	NS
Spanish as primary language (%)	38.0	14.8	<0.05
Hispanic ethnicity (%)	47.6	29.6	NS
Household income \$(mean ± SE)	47,609 ± 2800	56,087 ± 3368	NS
No medical insurance (%)	23.8	4.9	<0.05
<4/5 diagnostic criteria at diagnosis (%)	33.3	28.4	NS
No. of healthcare visits prior to diagnosis (mean ± SE)	3.7 ± 0.3	2.7 ± 0.2	<0.01
≥3 visits to any healthcare facility (%)	81.0	49.4	<0.01
≥1 emergency room/urgent care visit (%)	57.1	53.1	NS
≥1 private office visit (%)	52.4	43.2	NS
≥1 healthcare visit in Mexico (%)	19.0	4.9	<0.05
Hospitalized prior to diagnosis (%)	19.0	3.7	<0.05
Illness day at diagnosis (mean ± SE, range) *	12.6 ± 1.4, 4–28	7.2 ± 0.4, 2–21	<0.001

* Illness day 1 defined as the first day of fever.

CAA indicates coronary artery aneurysm; NS, not significant.

TABLE 2

Potential Risk Factors for Development of Coronary Artery Aneurysms in Patients With Acute Kawasaki Syndrome

Characteristic	Odds Ratio (95% confidence interval)	
	Model 1	Model 2
Spanish as primary language	2.0 (0.5–9.1)	2.0 (0.5–8.8)
No health insurance	3.3 (0.3–32.1)	4.0 (0.6–24.5)
≥1 healthcare visits in Mexico	1.1 (0.3–4.3)	—
Hospitalized prior to diagnosis	2.5 (0.5–11.9)	—
≥3 visits to any healthcare facility	—	2.4 (0.6–8.9)
Delayed diagnosis*	7.8 (2.4–25.1)	7.1 (2.2–23.3)

Two different logistic models were created: one set including specific healthcare facilities visited by the patient prior to obtaining a diagnosis of Kawasaki syndrome (Model 1) and one set including a summary measure of 3 or more visits to any and all healthcare facilities prior to obtaining a diagnosis (Model 2).

* Delayed diagnosis is defined as diagnosis after illness day 10. Illness day 1 is defined as the first day of fever.

TABLE 3

Characteristics of Patients With Acute Kawasaki Syndrome Diagnosed Before or After 10 Days of Illness

Characteristic	Diagnosis after Illness Day 10 (n = 28)	Diagnosis ≤ Illness Day 10 (n = 74)	P
Age (mo) (median, range)	11.3, 1.8–79.7	11.8, 1.8–138.4	NS
Males (%)	71.4	59.5	NS
No siblings (%)	20.8	21.7	NS
Spanish as primary language (%)	28.6	16.2	NS
Hispanic ethnicity (%)	35.7	32.4	NS
Household income (\$)(mean ± SE)	57,574 ± 5,004	53,133 ± 3,374	NS
No medical insurance (%)	14.3	6.8	NS
<4/5 diagnostic criteria at diagnosis (%)	46.4	23.0	<0.01
No. of healthcare visits prior to diagnosis (mean ± SE)	3.8 ± 0.3	2.5 ± 0.2	<0.001
≥3 visits to any healthcare facilities (%)	82.1	45.9	<0.001
≥1 emergency room/urgent care visit (%)	53.6	54.1	NS
≥1 private office visit (%)	35.7	48.6	NS
≥1 healthcare visit in Mexico (%)	14.3	5.4	NS
Hospitalized prior to diagnosis (%)	17.9	2.7	<0.01
Days to medical consultation (mean ± SE, range)*	3.9 ± 0.8, 1–20	2.8 ± 0.2, 3–24	NS
Days to diagnosis by physician (mean ± SE, range) [†]	10.7 ± 0.8, 0–9	3.0 ± 0.2, 0–19	<0.001

* Days to medical consultation defined as the time between illness day 1 and the patient's first healthcare contact.

[†] Days to diagnosis by physician defined as the time from the first healthcare contact to illness day at diagnosis. NS indicates not significant.

TABLE 4

Potential Risk Factors for Delayed Diagnosis* in Patients With Acute Kawasaki Syndrome

Characteristic	<u>Odds Ratio (95% confidence interval)</u>	
	Model 1	Model 2
<4/5 diagnostic criteria at diagnosis	2.8 (1.1–7.4)	3.0 (1.1–8.1)
Hospitalized prior to diagnosis	7.5 (1.3–43.4)	—
≥3 visits to any healthcare facilities	—	5.6 (1.9–16.7)

Two different logistic models were created: one set including specific healthcare facilities visited by the patient prior to obtaining a diagnosis of Kawasaki syndrome (Model 1) and one set including a summary measure of 3 or more visits to any and all healthcare facilities prior to obtaining a diagnosis (Model 2).

* Delayed diagnosis is defined as diagnosis after illness day 10. Illness day 1 is defined as the first day of fever.

TABLE 5
Potential Predictors of Delay in Patients With Acute Kawasaki Syndrome

Characteristic	Days to Medical Consultation [*]			Days to Diagnosis by Physician [†]		
	B	SE	P	B	SE	P
Age	-0.06	0.11	0.53	0.15	0.17	0.08
Male gender	-0.7	0.51	0.18	0.70	0.78	0.08
Spanish as primary language	-1.06	0.7	0.15	1.41	1.07	0.13
No health insurance	-0.04	0.98	<0.01	2.12	1.49	0.14
No of visits to other healthcare facilities	ND			1.12	0.24	0.41
<4 clinical signs	ND			0.77	0.38	0.18

^{*} Days to medical consultation defined as the time between illness day 1 and the patient's first healthcare contact.

[†] Days to diagnosis by physician defined as the time from the first healthcare contact to illness day at diagnosis. Illness day 1 is defined as the first day of fever.

B indicates unstandardized regression coefficient; SE, standardized regression coefficient; ND, not done.