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Kawasaki Disease at the Extremes of the Age Spectrum

Cedric Manlhiot, Rae S. M. Yeung, Nadia A. Clarizia, Nita Chahal and Brian W. McCrindle

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Kawasaki Disease at the Extremes of the Age Spectrum

WHAT'S KNOWN ON THIS SUBJECT: The majority of patients with KD are diagnosed between the ages of 1 and 4 years. Previous reports showed that children diagnosed outside this age range might be at higher risk for coronary artery abnormalities.

WHAT THIS STUDY ADDS: Suboptimal outcomes for children diagnosed with KD at both extremes of the age spectrum are equivalent. Increased physiological risk factors for young children highlight the importance of prompt treatment, whereas a greater index of suspicion is warranted for older children.

abstract

OBJECTIVE: We sought to determine outcomes of Kawasaki disease (KD) and to explore factors associated with poor clinical outcomes for patients diagnosed outside the age range of 1 to 4 years.

METHODS: A retrospective review of data for all patients seen between January 1990 and April 2007 was performed. Patients were stratified into 5 groups on the basis of age at diagnosis.

RESULTS: A total of 1374 patients were identified; 61 (4%) were <6 months of age at diagnosis, 114 (8%) 6 months to <1 year, 854 (62%) 1 to 4 years, 258 (19%) 5 to 9 years, and 87 (6%) >9 years. Patients <1 year of age and those >9 years of age were more likely to have coronary artery abnormalities than were patients diagnosed between 1 and 4 years of age. Patients diagnosed between the ages of 5 and 9 years were at the lowest risk. Patients at both extremes of the age spectrum were more likely to present with <4 of the classic KD features, but only those <6 months or >5 years of age were at increased risk of being diagnosed >12 days after illness onset. Patients <6 months of age had lower albumin levels, and those <1 year of age had higher white blood cell and platelet counts, all of which are known predictors of coronary artery abnormalities. Patients >9 years of age were less likely to receive intravenous immunoglobulin treatment.

CONCLUSION: Outcomes for children diagnosed with KD at either extreme of the age spectrum are suboptimal, although the associated factors are different. *Pediatrics* 2009;124:e410–e415

CONTRIBUTORS: Cedric Manlhiot, BSc,[a] Rae S. M. Yeung, MD, PhD,[b] Nadia A. Clarizia, BSc,[a] Nita Chahal, MN, CNS-NP,[a] and Brian W. McCrindle, MD, MPH[a]

Divisions of [a]Cardiology and [b]Rheumatology, Department of Pediatrics, University of Toronto, Labatt Family Heart Centre, Hospital for Sick Children, Toronto, Ontario, Canada

KEY WORDS

Kawasaki disease, epidemiology, coronary artery abnormalities

ABBREVIATIONS

KD—Kawasaki disease
IVIG—intravenous immunoglobulin

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Address correspondence to Brian W. McCrindle, MD, MPH, Department of Pediatrics, Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada. E-mail: brian.mccrindle@sickkids.ca

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The majority of children with Kawasaki disease (KD) are diagnosed between the ages of 1 and 4 years. Although KD is less prevalent at other ages, children as young as 1 month of age and adults in their early 20s have been diagnosed as having KD.[1] Patients who are diagnosed at these extremes of the age spectrum, especially those <6 months of age and adolescents, are thought to be at higher risk of coronary artery abnormalities after KD.[2–6] The greater incidence of coronary artery abnormalities at the extremes of the age spectrum is most likely multifactorial in nature, with a greater frequency of patients presenting without all of the classic KD clinical features. This may make the diagnosis challenging and may contribute to longer delays from symptom onset to appropriate treatment for these children.[7,8] Such delays are associated with greater odds of coronary artery sequelae.[9] Previous studies explored clinical differences for specific age groups in limited cohorts of patients with KD and compared those groups with the rest of the patient populations.[2–5] Few studies compared clinical characteristics and outcomes for multiple age groups in a large contemporary cohort of patients with KD.[6] This study compares clinical characteristics, treatment, and outcomes for children with KD by using age stratification spanning the entire age spectrum.

METHODS

The medical records for all children with a diagnosis of KD who were seen at the Hospital for Sick Children between January 1990 and April 2007 were reviewed. The study was approved by the hospital research ethics board, and the requirement for individual consent was waived for the retrospective study. Patients were divided into 5 categories on the basis of their age at diagnosis, that is, <6 months, 6 months to <1 year, 1 to 4 years, 5 to 9 years, and >9 years of age.

Complete KD presentation was defined as fever for ≥5 days and ≥4 of the following classic KD clinical signs: bilateral conjunctival injection, cervical lymphadenopathy, polymorphous skin rash, changes in the lips or oral mucosa, and changes (edema/peeling) of the extremities. Patients with fever for ≥5 days and 2 or 3 KD clinical signs were considered to have incomplete presentations.[1] The diagnoses for these patients were confirmed by ≥2 pediatricians (including ≥1 KD specialist), and the patients were treated in the same manner as all other patients with KD. The time from fever onset to intravenous immunoglobulin (IVIG) treatment was used as a surrogate measure for difficulties and/or delays in obtaining the correct diagnosis. The total number of days of fever was defined as the number of days between fever onset and defervescence (body temperature of <38°C).

Coronary artery abnormalities attributable to KD were defined on the basis of a coronary artery branch internal lumen diameter either meeting the Japanese Ministry of Health criteria or having a diameter *z* score of ≥2.5, with adjustment for body surface area. The Japanese Ministry of Health defines coronary artery abnormalities as any coronary artery branch being internal lumen diameter ≥3 mm for children <5 years of age or ≥4 mm for children ≥5 years of age or the internal diameter of any branch being >1.5 times greater than that of any adjacent segment.[10] Coronary artery abnormalities of ≥5 mm, regardless of age, and/or those with body surface area-adjusted *z* scores of ≥5 were classified as aneurysms. The maximal coronary artery *z* score was taken as the highest coronary artery *z* score among the right main coronary artery, the left main coronary artery, and the left anterior descending coronary artery.[1,11] According to institutional protocol, patients underwent standardized echocardiograms during the acute phase and 6 to 8 weeks later, in cardiology clinic follow-up evaluations.

Data are presented as means with SDs, medians with ranges, or frequencies as appropriate. Differences among the 5 age groups with respect to demographic, clinical, laboratory, and treatment characteristics were estimated with multiple univariate linear (for continuous outcomes) and logistic (for binary outcomes) regression models, by using the age at diagnosis as the independent variable and the 1- to 4-year-old category as the reference category. Appropriate mathematical transformations were applied to variables with nonnormal distributions. All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 1374 patients were identified. Of those, 61 (4%) were <6 months of age at diagnosis, 114 (8%) were 6 months to <1 year of age, 854 (62%) were 1 to 4 years of age, 258 (19%) were 5 to 9 years of age, and 87 (6%) were >9 years of age. There were comparable proportions of boys in all age groups (60%–74%). Complete demographic, clinical, and laboratory characteristics are detailed in Table 1. Children <1 year of age and those >9 years of age were more likely to present with only 2 or 3 KD clinical signs and to be classified as having incomplete presentation. Laboratory investigations showed differences between groups for all markers except hematocrit levels, red blood cell counts, and albumin levels, which were lower for patients <6 months of age but were similar for all other age groups. Patients who were <1 year of

TABLE 1 Demographic, Clinical, and Laboratory Features of Patients With KD According to Age

	Age <0.5 y		Age 0.5 to <1 y		Age 1–4 y		Age 5–9 y		Age >9 y		*P*			
	N	Parameter	*N*	Parameter	*N*	Parameter	*N*	Parameter	*N*	Parameter	<0.5 y vs 1–4 y	0.5 to <1 y vs 1–4 y	5–9 y vs 1–4 y	>9 y vs 1–4 y
Male, *n* (%)	61	45 (74)	114	79 (69)	854	502 (62)	258	154 (60)	87	58 (67)	.06	.11	.43	.44
Bilateral conjunctival injection, *n* (%)	56	50 (89)	105	92 (88)	755	676 (90)	244	214 (88)	83	70 (84)	.95	.55	.43	.16
Cervical lymphadenopathy, *n* (%)	56	22 (39)	105	49 (47)	755	486 (65)	244	179 (73)	83	49 (59)	<.001	<.001	.02	.31
Lips/oral mucosa changes, *n* (%)	56	44 (79)	105	92 (88)	755	683 (90)	244	211 (86)	83	73 (88)	.005	.32	.08	.47
Polymorphous skin rash, *n* (%)	56	53 (95)	105	99 (94)	755	670 (89)	244	211 (86)	83	69 (83)	.20	.10	.34	.14
Extremity changes, *n* (%)	56	36 (64)	105	81 (77)	755	593 (79)	244	196 (80)	83	63 (76)	.02	.68	.56	.58
Fever for ≥5 d and ≤3 clinical signs, *n* (%)	58	21 (36)	110	37 (34)	781	172 (22)	248	58 (23)	86	31 (36)	.02	.008	.65	.004
Albumin level, mean ± SD, g/L	47	32 ± 6	85	36 ± 7	591	36 ± 5	187	35 ± 6	62	37 ± 8	<.001	1.00	.42	1.00
Alanine transaminase level, median (range), U/L	46	25 (3–161)	82	27 (3–508)	583	27 (3–2483)	190	23 (3–1004)	64	34 (7–467)	<.001	<.001	<.001	.02
Aspartate transaminase level, median (range), U/L	43	31 (8–188)	78	32 (13–318)	573	38 (14–1000)	187	34 (3–406)	64	44 (12–229)	<.001	<.001	<.001	.12
C-reactive protein level, mean ± SD, mg/L	30	25 ± 5	67	29 ± 5	440	69 ± 34	138	42 ± 16	50	60 ± 19	<.001	<.001	<.001	<.001
Erythrocyte sedimentation rate, median (range), mm/h	43	72 (1–132)	85	70 (1–130)	631	72 (1–145)	203	75 (1–169)	65	52 (1–132)	<.001	.009	.002	<.001
Hematocrit level, mean ± SD	54	0.295 ± 0.031	95	0.316 ± 0.030	648	0.329 ± 0.033	213	0.345 ± 0.034	68	0.366 ± 0.043	.67	.83	.74	.63
Hemoglobin level, mean ± SD, g/L	55	100 ± 11	95	107 ± 11	663	111 ± 11	215	117 ± 11	69	123 ± 15	<.001	<.001	<.001	<.001
Lymphocyte count, median (range), 10^9 cells per L	51	5.3 (0.4–14.5)	94	4.4 (0.1–13.4)	645	2.9 (0.2–13.3)	211	1.6 (0.1–8.0)	67	1.1 (0.1–6.5)	<.001	<.001	<.001	<.001
Platelet count, median (range), 10^9 cells per L	55	482 (119–1036)	96	408 (94–1419)	660	359 (60–1461)	213	310 (69–1054)	69	268 (86–620)	<.001	<.001	<.001	<.001
Red blood cell count, mean ± SD, 10^{12} cells per L	30	3.8 ± 0.5	68	4.2 ± 0.5	461	4.2 ± 0.5	154	4.2 ± 0.5	52	4.5 ± 0.6	<.001	1.00	.98	.43
White blood cell count, mean ± SD, 10^9 cells per L	53	18.4 ± 7.6	97	15.3 ± 6.0	657	13.6 ± 5.7	213	13.1 ± 6.3	69	12.2 ± 7.4	<.001	<.001	.08	.003

age had lower hemoglobin levels and higher platelet counts than did patients who were >1 year of age. Patients who were >4 years of age at diagnosis had favorable laboratory profiles, with higher hemoglobin levels and lower platelet counts, compared with children who were <4 years of age at diagnosis.

Compared with patients who were 1 to 4 years of age at diagnosis, the median duration of fever before IVIG treatment was greater for all other age groups except the group 6 months to 1 year of age (Table 2). In addition, patients <6 months of age and those >4 years of age were significantly more likely to receive diagnoses >12 days after symptom onset. Patients >4 years of age also were less likely receive IVIG treatment, and those >9 years of age were more likely to require multiple IVIG treatments and treatment with steroids (Table 3). Patients diagnosed at <6 months of age and those diagnosed at >9 years of age were more likely to develop coronary artery aneurysms than were those diagnosed at 1 to 4 years of age. Patients who were 5 to 9 years of age at diagnosis had the best coronary artery outcomes of all age groups, with 87% of patients having no coronary artery abnormalities, compared with 80% for patients 1 to 4 years of age at diagnosis, 75% for patients >9 years of age, 75% for patients 6 months to <1 year of age, and 48% for patients <6 months of age.

DISCUSSION

In comparing 5 age strata in a contemporary cohort of children diagnosed as having KD, we found that children <6 months of age at presentation and those >9 years of age had increased risks of coronary artery aneurysms but with different associated factors. Children presenting before 6 months of age were found to have many laboratory features known to be associ-

TABLE 2 Clinical History and Treatment of Patients With KD According to Age

	Age <0.5 y		Age 0.5 to <1 y		Age 1–4 y		Age 5–9 y		Age >9 y		*P*			
	N	Parameter	*N*	Parameter	*N*	Parameter	*N*	Parameter	*N*	Parameter	<0.5 y vs 1–4 y	0.5 to <1 y vs 1–4 y	5–9 y vs 1–4 y	>9 y vs 1–4 y
Diagnosis >12 d after onset, *n* (%)	56	14 (25)	105	9 (9)	715	75 (10)	229	36 (16)	73	15 (21)	.002	.59	.04	.02
Duration of fever before IVIG treatment, median (range), d	53	7 (3–46)	101	6 (3–30)	660	6 (2–33)	198	7 (3–63)	65	7 (4–21)	<.001	.71	<.001	.02
Antibiotic treatment before diagnosis, *n* (%)	57	30 (53)	112	46 (41)	787	343 (44)	251	134 (53)	86	39 (45)	.13	.83	.007	.76
IVIG treatment, *n* (%)	61	59 (97)	112	103 (92)	772	692 (90)	242	205 (85)	84	68 (81)	.08	.35	.04	.02
Aspirin treatment, *n* (%)	60	60 (100)	112	107 (96)	777	749 (96)	247	236 (96)	83	77 (93)	1.00	.80	.54	.12
Multiple IVIG treatments, *n* (%)	60	9 (15)	111	16 (14)	768	69 (9)	237	26 (11)	84	14 (17)	.12	.07	.36	.03
Intravenous steroid treatment, *n* (%)	60	7 (12)	111	5 (5)	768	25 (3)	237	10 (4)	84	8 (10)	.001	1.00	.49	.008
Oral steroid treatment, *n* (%)	60	4 (7)	111	0 (0)	768	6 (1)	237	4 (2)	84	4 (5)	.02	.98	.23	.005

ated with coronary artery abnormalities, such as lower albumin levels, lower hemoglobin levels, higher platelet counts, and longer times from disease onset to diagnosis, but a similar likelihood of IVIG treatment and equivalent duration of fever after initiation of appropriate treatment, compared with children diagnosed at 1 to 4 years of age. In comparison, children >9 years of age had favorable laboratory profiles, compared with younger patients, but had longer delays from fever onset to diagnosis, were more likely to be diagnosed >12 days after symptom onset, were less likely to be treated with IVIG, and, for those who were treated with IVIG, had longer duration of fever after treatment. This study supports the hypothesis that, although the 2 groups are equally susceptible to coronary artery abnormalities after KD, children <6 months of age are more likely to have pathophysiological factors associated with the development of coronary artery abnormalities. Coronary artery outcomes for children >9 years of age were more likely to be associated with difficulties and subsequent delays in diagnosis and a lower rate of receiving appropriate treatment. The coexistence of 2 sets of associated factors (pathophysiological and clinical) for children diagnosed at <6 months of age might explain the worse outcomes for this population, compared with all other age groups.

Patients in our population were similar to the general KD population with respect to characteristics and age distribution, with 75% of patients being diagnosed at <5 years of age and most being diagnosed at 1 to 4 years of

TABLE 3 Clinical and Cardiac Outcomes for Patients With KD According to Age

	Age <0.5 y		Age 0.5 to <1 y		Age 1–4 y		Age 5–9 y		Age >9 y		*P*			
	N	Parameter	*N*	Parameter	*N*	Parameter	*N*	Parameter	*N*	Parameter	<0.5 y vs 1–4 y	0.5 to <1 y vs 1–4 y	5–9 y vs 1–4 y	>9 y vs 1–4 y
Clinical outcomes														
Fever after IVIG treatment, median (range), d	53	1 (1–15)	101	1 (1–9)	660	1 (0–22)	198	1 (0–9)	65	1 (1–27)	.03	.48	.79	<.001
Total duration of fever, median (range), d	55	9 (4–47)	105	7 (3–31)	744	8 (3–37)	236	8 (3–64)	80	9 (5–42)	<.001	.69	<.001	<.001
Hospitalization, median (range), d	54	7 (2–76)	105	4 (2–22)	706	4 (2–51)	214	4 (2–49)	69	5 (2–43)	<.001	.04	<.001	<.001
Coronary artery abnormalities														
No coronary artery abnormalities, *n* (%)	61	29 (48)	114	85 (75)	854	665 (80)	258	225 (87)	87	65 (75)	<.001	.12	.005	.12
Coronary artery dilation only, *n* (%)	61	10 (16)	114	22 (19)	854	113 (14)	258	21 (8)	87	13 (15)	.44	.08	.02	.75
Coronary artery aneurysms, *n* (%)	61	22 (36)	114	7 (6)	854	36 (4)	258	12 (5)	87	9 (10)	<.001	.33	.86	.04

age.[1,12] Previous reports focused separately on patients at the 2 extremes of the age spectrum. Studies of children <1 year of age found that such patients were more likely to have incomplete presentation and were at greater risk of coronary artery abnormalities.[2–4] In 2 small studies of older children with KD, similar increases in rates of coronary artery abnormalities were observed, which might have been associated with longer delays in diagnosis.[5,6] Sample sizes in those previous studies were limited, and no studies compared the age extremes with one another.

Contradicting studies have reported that patients presenting with <4 of the classic KD clinical signs could be at higher risk for coronary artery abnormalities after KD.[13] Recent studies showed that, although the association probably is accurate, incomplete presentation was associated with greater delays from fever onset to diagnosis and children with incomplete presentation were less likely to be treated with IVIG. This could explain, in part, the observed association.[8] Longer time from symptom onset to appropriate treatment has been shown to be associated with greater probability of coronary artery abnormalities.[9] In this cohort, incomplete presentation was more likely for children <1 year of age and those >9 years of age than for children diagnosed in the usual range of 1 to 4 years of age. However, only children <6 months of age and those >5 years of age were found to be at increased risk of being diagnosed at >12 days of illness, which suggests the need for a higher index of suspicion for KD in these age groups. A study of physicians' practices in diagnosing KD in the United States found that >50% of general pediatricians and 25% of infectious disease specialists do not consider the diagnosis of KD for children >8 years of age.[7] The diagnosis remains a challenge in older children, in part because of the higher likelihood of incomplete presentation for this population but also because of a lack of suspicion on the part of physicians. Both the timing of treatment and laboratory markers are associated with coronary artery abnormalities in KD. A large array of laboratory markers have been reported to be associated with increased risk of coronary artery abnormalities in this population, but few have been reported consistently across studies. The 3 factors reported most commonly are lower albumin level, lower hemoglobin level, and higher platelet count.[9,14] Our study found that children diagnosed at <6 months of age had the least favorable laboratory profiles of all groups, whereas those >9 years of age had the most favorable profiles. Children diagnosed at 6 months to 1 year or 5 to 9 years of age had intermediate profiles. This finding might be counterintuitive in relation to previous studies of risk factors for coronary artery lesions, because older children had both increased risk of coronary artery abnormalities and more-favorable laboratory profiles. Future studies investigating the risk factors for coronary artery abnormalities in KD ought to take into consideration patient age at diagnosis and other factors, because laboratory markers associated with poor coronary artery outcomes might differ between age groups.

Patients who were >9 years of age at diagnosis were less likely to be treated with IVIG, and those who were treated were more likely to require repeated IVIG treatment, to require steroid treatment, and to have a longer duration of fever after initial IVIG infusion. This unusual observation warrants further investigation.[15] Compared with children 1 to 4 years of age, children >5 years of age had similar clinical profiles (albeit worse for >9 years of age than for 5–9 years of age), but patients 5 to 9 years of age did not have increased risk of coronary artery abnormalities. This might reflect a potential threshold in duration of fever before treatment, after which the risk of coronary artery abnormalities increases. With this perspective, patients 5 to 9 years of age might have benefited from their more-favorable laboratory profile but were not affected as much by the less-extreme delays in diagnosis, beyond which the risk of coronary artery abnormalities increases.

This study must be viewed in light of some potential limitations inherent in its retrospective design, although the amounts of missing data are limited and the large sample ensured adequate amounts of data available for analysis. Also, it is not possible to exclude the possibility that some patients with incomplete presentation might have had not KD but another illness with similar clinical signs.

By examining the entire spectrum of ages at KD diagnosis, rather than focusing on a single age group, our study was able to demonstrate that patients at both extremes of the age spectrum were at increased risk for coronary artery abnormalities, albeit with different associated factors. Younger patients were found to have unfavorable laboratory profiles for coronary artery abnormalities and were at high risk despite being treated with IVIG. At the other extreme, older patients were less likely to receive appropriate treatment and were more likely to receive treatment later, compared with patients 1 to 4 years of age at the time of KD diagnosis. This study suggests that strategies to prevent coronary artery abnormalities associated with KD be tailored to patient age at diagnosis. Younger patients might benefit from more-aggressive treatment and a lower threshold for retreatment, especially in the presence of other risk

factors for coronary artery abnormalities. Older patients might benefit from a higher index of suspicion at the level of primary care, with the aim of reducing the delay between symptom onset and appropriate treatment. Increased risk factors for suboptimal outcomes for young children highlight the importance of prompt treatment, whereas a greater index of suspicion for the diagnosis is warranted for older children.

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