High Risk of Coronary Artery Aneurysms in Infants Younger than 6 Months of Age with Kawasaki Disease

Andrea P. Salgado, MD[1], Negar Ashouri, MD[2], Erika K. Berry, BA[1], Xiaoying Sun, MS[3], Sonia Jain, PhD[3], Jane C. Burns, MD[4], and Adriana H. Tremoulet, MD[4]

Objectives To characterize the clinical presentation and outcome in infants <6 months of age with Kawasaki disease (KD) and to describe the use of newer anti-inflammatory therapies in this young population.

Study design We evaluated 88 infants <6 months old and 632 ≥6 months old treated for KD. We compared differences in laboratory data, response to treatment, and coronary artery outcomes between the 2 cohorts. Fisher exact test was used to analyze categorical variables, whereas the Wilcoxon rank sum test was used for continuous variables.

Results The majority of children in both cohorts were diagnosed and treated within the first 10 days of illness (median illness day 6 in both cohorts). For patients treated within the first 10 days after fever onset, a larger proportion of infants <6 months old had a dilated or aneurysmal coronary artery on the initial echocardiogram compared with those ≥6 months old (43.4% vs 19.5%). Furthermore, 18.6% of infants <6 months old who had a normal echocardiogram at diagnosis, developed a dilated or aneurysmal coronary artery on a subsequent echocardiogram within 8 weeks of diagnosis. Twenty-eight infants <6 months old received a single dose of infliximab without any untoward effects.

Conclusions Despite treatment in the first 10 days, infants <6 months old with acute KD are more likely to develop coronary artery abnormalities. Thus, the development of adjunctive therapies to reduce coronary artery damage should target this population. *(J Pediatr 2017;185:112-6).*

Infants <6 months of age are reported to have a higher prevalence of incomplete Kawasaki disease (KD), delayed diagnosis and treatment, coronary artery abnormalities, and intravenous immunoglobulin (IVIG) resistance.[1-7] These adverse outcomes may be intertwined as incomplete clinical signs can lead to delayed diagnosis, late treatment, and increased risk of aneurysms that develop in up to 25% of untreated or late treated patients with KD. However, limited information is available for this population. The aims of this study were to characterize the clinical presentation and outcome in infants with KD <6 months of age and to describe the use of newer anti-inflammatory therapies in this young population.

Methods

We evaluated 88 infants <6 months old and 632 ≥6 months old treated for KD between January 1, 2004 and December 31, 2013. Of the 88 infants, 53 were treated at Rady Children's Hospital San Diego (RCHSD) and had data prospectively collected, whereas 35 had data collected retrospectively at Children's Hospital Orange County (CHOC). All of the patients ≥6 months were treated at RCHSD and had data prospectively collected. We collected demographic and clinical data, including age, ethnicity, illness day at diagnosis (illness day 1 = first day of fever), response to IVIG therapy, coronary artery status, complete blood count, erythrocyte sedimentation rate, and plasma concentrations of C-reactive protein (CRP), alanine aminotransferase (ALT), and γ-glutamyl transferase prior to IVIG treatment. We age-adjusted hemoglobin concentrations and expressed the values as SDs from the mean (zHgb) according to the following formula: ([observed hemoglobin] – [mean hemoglobin for age])/SD for age.[8] The SDs were estimated

AHA	American Heart Association
CHOC	Children's Hospital Orange County
CRP	C-reactive protein
KD	Kawasaki disease
IVIG	Intravenous immunoglobulin
LAD	Left anterior descending artery
RCA	Right coronary artery
RCHSD	Rady Children's Hospital San Diego

From the [1]Pontificia Universidad Catolica de Chile, Santiago, Chile; [2]Children's Hospital, Orange County, CA; [3]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA; and [4]Department of Pediatrics, University of California, San Diego, California/Rady Children's Hospital San Diego, La Jolla, San Diego, CA

Supported by the National Heart, Lung, and Blood Institute (HL69413 and K24 HL074864 [to J.B.]), Rady Children's Hospital San Diego Physician Development Fund (to A.T), the National Center for Research Resources/the National Center for Advancing Translational Sciences (UL1 TR001414 [to A.T.]), and The Macklin Foundation. The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.03.025

as one-quarter of the reported range of normal hemoglobin concentrations for each age interval.

Complete KD presentation was defined as fever ≥3 days and ≥4 of the following clinical signs: bilateral conjunctival injection, polymorphous skin rash, changes in the lips or oral mucosa, changes (edema/redness/peeling) of the extremities, and unilateral cervical lymphadenopathy. Patients with fever ≥3 days plus ≤4 criteria with or without echocardiogram abnormalities were classified as incomplete KD. The response to IVIG therapy was classified as resistant, responsive, late treatment (≥11 days after fever onset), not treated, or unevaluable (received infliximab in addition to IVIG as initial therapy either for coronary artery aneurysms or because of clinical trial participation). IVIG-resistance was defined as persistent or recrudescent fever (temperature ≥38.0°C rectally or orally) at least 36 hours but not longer than 7 days after completion of the first IVIG infusion.

Echocardiograms were performed according to a standard protocol applied to all patients with KD. The standard of care at both centers is to perform an echocardiogram at the time of initial diagnosis and at 2 weeks after diagnosis in all patients with KD. In addition, infants and children with coronary artery damage have echocardiograms performed more frequently and at similar intervals (ie, every 1-2 weeks depending on severity of illness) as part of standard of care at both institutions. Patients were classified at RCHSD as having normal (<2.5 SD units [z score] from the mean, normalized for body surface area), dilated (z score ≥2.5 to <4), or aneurysmal (z ≥ 4; z > 10 for giant aneurysm) coronary arteries on the basis of the maximal internal diameters of the right coronary artery (RCA) and left anterior descending artery (LAD) measured by echocardiography at the time of diagnosis and up to 8 weeks after onset of fever. The worst-ever z score (z worst) for either the RCA or LAD at any time point during the first 6 weeks after fever onset or the z score of the largest aneurysm in any coronary artery segment was used for the continuous variable analysis. Body surface area and z scores were calculated using the Haycock and the Dallaire equations, respectively.[9] At CHOC, coronary artery abnormalities were classified as normal, dilated, or aneurysmal (focal dilation of an arterial segment at least 1.5 times the diameter of the adjacent segment). The study received Institutional Review Board approval at the University of California, San Diego and CHOC.

Statistical Analyses

The data for infants <6 months old were combined for the 2 sites and compared with infants and children ≥6 months old. Worst z score on any echocardiogram among patients was compared for infants <6 months old vs those ≥6 months old for RCHSD only as z score data were not available for CHOC. Fisher exact test was used to analyze categorical variables, whereas the Wilcoxon rank sum test was used for continuous variables.

For laboratory values that were outside the dynamic range of the test (ie, erythrocyte sedimentation rate of ≥140 mm/hour, ALT ≤3 mg/dL, and CRP ≤0.3 mg/dL), the maximal or minimal value detected by the assay was used, as appropriate. All statistical analyses were performed in the statistical software R v 3.1.0 (available at: http://www.R-project.org). No adjustments were made for multiple testing. *P* values less than .05 were considered statistically significant.

Results

Of the patients in this study, 88 (12.2%) were <6 months old at the time of diagnosis with KD and the remaining 632 patients (87.8%) were between 6 months and 17 years old (**Table I**). As is seen typically in KD, a predominance of the patients were male in both cohorts. There were more patients with KD of Asian ethnicity in the <6-month-old cohort and a larger number of patients that were of mixed racial background in those ≥6 months of age. Both cohorts had a median illness day of 6 days at the time of diagnosis, and the majority in both cohorts (86.4% in <6-month-old group and 86.2% in ≥6-month-old group) were diagnosed and treated within the first 10 days of illness.

Overall, oral changes, unilateral cervical lymphadenopathy, and extremity changes were more common in the older group (*P* = .04, <.001, and <.001, respectively) (**Table I**). Although there was a larger proportion of patients with complete KD at RCHSD (33/53, 62.3%) than at CHOC (12/35, 34.3%), this proportion was higher for patients older than 6 months of age (505/632, 79.9%). Patients <6 month old were more likely to be diagnosed based on an abnormal baseline echocardiogram than by laboratory evaluation as per the 2004 American Heart Association (AHA) KD guidelines (**Table I**). With respect to laboratory data, the median white blood cell, platelet count, and CRP were higher and ALT and albumin were lower in the <6-month-old group (**Table I**). We also compared the demographic, clinical, and laboratory data between infants <6 months old with and without coronary artery abnormalities; there were no significant differences in sex, ethnicity, clinical presentation, and baseline laboratory data between these 2 groups.

All patients were treated with IVIG (2 g/kg) and aspirin except for patients who presented late in the course of illness and no longer had evidence of systemic inflammation (2 of 88 < 6 months old (2.3%); 17 of 632 ≥ 6 months old (2.7%)) (**Table I**). At RCHSD, the clinical practice was to administer infliximab (5 mg/kg) to all patients with an initial RCA or LAD z score ≥2.5 and as the first re-treatment for IVIG-resistance. At CHOC, the clinical practice was to administer infliximab to all patients with a coronary artery dilatation or aneurysm and to administer a second dose of IVIG for IVIG-resistance. Infants <6 months old were more likely to receive infliximab for coronary artery dilation by echocardiogram compared with those ≥6 months old who were more likely to have received infliximab as part of a phase III clinical trial. Of the 86 infants treated with IVIG, 22 (25.6%) received infliximab within 36 hours of IVIG either as part of a phase III clinical trial (n = 5, 22.7%) or for a dilated or aneurysmal coronary artery on the first echocardiogram (n = 17, 77.3%) (**Figure 1**; available at www.jpeds.com). At the 2 sites combined, a total of 28 infants <6 months old received a single dose of infliximab without any untoward effects at either the time of administration or over