Marked Variations in Serial Coronary Artery Diameter Measures in Kawasaki Disease: A New Indicator of Coronary Involvement

Frédéric Dallaire, MD, PhD, Anne Fournier, MD, Jolène Breton, MS, Thanh-Diem Nguyen, MD, Linda Spigelblatt, MD, and Nagib Dahdah, MD, *Montreal, Quebec, Canada*

Background: The long-term risk of patients with Kawasaki disease is not well defined. A great proportion of patients with Kawasaki disease have important variation of their coronary artery (CA) diameters, but the significance of this variation is not known. The aim of this study was to test the hypothesis that patients within the normal range of CA diameters but with important *Z*-score variation have a stronger inflammatory response and increased resistance to treatment than those without such *Z*-score variation.

Methods: A retrospective study was conducted in 197 patients with Kawasaki disease with serial echocardiograms up to 12 months after diagnosis. Patients with occult CA dilatation (variation > 2 *Z*-score units but within the normal range) were compared with patients with definite CA dilatation (*Z* score > 2.5) and with patients with normal CA for resistance to treatment and systemic inflammatory parameters.

Results: A total of 63 patients (32.0%) were identified with *Z* scores always within the normal range but with important variation of CA diameter during follow-up (occult dilatation). There was a strong statistically significant trend of increasing inflammatory marker levels across patient categories (normal > occult dilatation > definite dilatation). Furthermore, resistance to intravenous immunoglobulin therapy was significantly increased in patients with occult dilatation compared with patients with normal CAs (relative risk, 2.6; 95% confidence interval, 1.21–5.44; $P = .006$).

Conclusions: The suggested definition of occult CA dilatation identified patients with CA involvement currently unrecognized per the current guidelines. These patients might be at a higher CA risk than previously thought. (J Am Soc Echocardiogr 2012;25:859-65.)

Keywords: Mucocutaneous lymph node syndrome, Intravenous immunoglobulins, Coronary aneurysm, Coronary artery disease, Echocardiography, Inflammation

Kawasaki disease (KD) is a childhood acute vasculitis for which an etiology has not yet been identified. Coronary artery (CA) involvement is the principal complication of KD, spanning from dilatation to aneurysm formation, the latter potentially leading to ischemic heart disease. The aim of current treatment remains the reduction of CA injury by controlling the systemic inflammatory response.[1] The definition of CA dilatation has been evolving. Dichotomous cutoffs to differentiate between normal and abnormal CA dimensions have been used,[2,3] but some authors have subsequently suggested that *Z* scores should be used to detect coronary dilatation in patients with KD.[4,5]

Not all children with KD develop CA aneurysms, but it has been demonstrated that transient dilatation of CAs frequently occurs[6] and that the magnitude of CA dimension variation during KD could be associated with risk factors for subsequent coronary involvement.[5] We thus hypothesized that in patients with KD, a large variation of CA dimensions between the acute phase and late follow-up could be used to detect CA involvement currently unrecognized per the current recommendations. This would avoid the misclassification of patients with KD with relatively small baseline CAs in the lowest long-term risk category when they do not attain the proposed *Z* score cutoff value of 2.5. To support this, we tested the hypothesis that patients with so-called normal CAs but with large variation of their CA dimension between the acute phase and the first year of follow-up (i.e., patients with occult CA dilatation) would have an increased inflammatory response and increased resistance to treatment compared with patients without such variation. We thus sought to correlate the level of inflammation and resistance to treatment with CA dimension variations using serial echocardiographic studies in patients with KD.

From the Division of Pediatric Cardiology, Department of Pediatrics, Laval University Hospital, Faculty of Medicine, Laval University, Quebec, Quebec, Canada (F.D.); the Division of Pediatric Cardiology, Sainte-Justine University Hospital Center, University of Montreal, Montreal, Quebec, Canada (F.D., A.F., J.B., T.-D.N., N.D.); and the Department of Pediatrics, Hôpital Maisonneuve-Rosemont, Montreal, Quebec, Canada (L.S.).

Reprint requests: Nagib Dahdah, MD, Division of Pediatric Cardiology (6 Bloc 9), CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Montreal, QC H3T 1C5, Canada (E-mail: *nagib.dahdah.hsj@ssss.gouv.qc.ca*).

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Abbreviations
CA = Coronary artery
CI = Confidence interval
IQR = Interquartile range
IVIG = Intravenous immunoglobulin
KD = Kawasaki disease
LMCA = Left main coronary artery
RCA = Right coronary artery

METHODS

Population

We retrospectively identified children who were diagnosed with complete or incomplete KD at the Sainte-Justine Children's Hospital (Montreal, QC, Canada) or at the Maisonneuve-Rosement Hospital (Montreal, QC, Canada) between August 1999 and February 2010. Because KD with incomplete criteria cannot be objectively ruled in or out, patients were eligible if the suspicion of KD was such that treatment with intravenous immunoglobulin (IVIG) was deemed clinically indicated by the attending physician. We excluded children with uncorrected significant structural heart anomalies. Charts were reviewed for information on presenting signs and symptoms, fever duration, the type and timing of treatment, and demographic characteristics. We retrieved the first laboratory results available upon diagnosis for white blood cell count, C-reactive protein, albumin, platelets, and the erythrocyte sedimentation rate. The need for a second IVIG course was based on the persistence of fever >48 hours after initial IVIG treatment. CA *Z*-score variation was not a criterion for repeated treatment. Treatment with aminosalicylates, steroids, and anticoagulation was in accordance with current recommendations.[1] This study received institutional approval.

Echocardiographic Studies

Serial echocardiographic studies are routinely performed for all patients with KD at the participating institutions, and all measurements are prospectively entered in our echocardiography database. CAs were measured at diagnosis; at 1, 2, and 3 weeks; at 2 and 3 months; and between 6 and 12 months after diagnosis by experienced sonographers specifically trained for CA measurements in our laboratory. The intraluminal diameters of CA segments were measured from inner edge to inner edge. The left main CA (LMCA) was measured midway between the ostium and the bifurcation of the circumflex artery and the left anterior descending CA in the parasternal short-axis view. Proximal right CA (RCA) measurements were obtained 3 to 5 mm distal to its origin in the parasternal short-axis view. In case of CA ectasia or aneurysms, the portion with the largest diameter was measured instead. A random sample of 20 patients was selected for intraobserver and interobserver variation. Each coronary segment was measured by two blinded sonographers and twice by the same sonographers on two different occasions.

Z Scores and Classification

Height and weight were measured each time echocardiography was performed. Body surface area was estimated using the method of Haycock *et al.*[7] CA measurements in our database were used to recalculate *Z* scores using equations recently published by our group.[8]

Three mutually exclusive patient categories were defined as follows. For each patient, we first identified the highest observed *Z* score for a given CA segment. Patients with *Z* scores > 2.5 at any time for the LMCA or RCA were included in the "definite CA dilatation" category. For the remaining patients, we determined the difference between their highest *Z* scores and the subsequent lowest *Z* score for each CA segment. When this difference was >2.0, patients were categorized as having "occult CA dilatation." This category thus included patients with increased CA diameters (not considered dilated per the current criteria) followed by an important reduction of that diameter during follow-up. Finally, the remaining patients were considered as having normal CAs (i.e., *Z* scores always < 2.5 with *Z*-score variation never > 2.0).

Because the cutoff of 2.0 *Z*-score units of difference used to categorize patients in the occult dilatation category was arbitrary, we also analyzed our data when different cutoff values were used (1.0, 1.5, and 2.5).

Statistical Analysis

Most continuous variables failed the normality test. Consequently, they are presented as medians and interquartile ranges (IQR) and were analyzed using nonparametric statistical tests. The two-tailed nonparametric Wilcoxon rank-sum test was used for two-group comparison of continuous variables. The Kruskal-Wallis test was used when more than two continuous variables were compared. Fisher's exact test was used to compare categorical variables. We also used the nonparametric Jonckheere-Terpstra test to detect trends between dilatation categories. This test was designed to test the hypothesis that population medians follow a particular trend ($\text{median}_1 \leq \text{median}_2 \leq \text{median}_3$).[9] In our study, categories were ordered as follows: normal ≤ occult dilatation ≤ definite dilatation. Finally, logistic regression was used to assess the probability of resistance to treatment according to dilatation categories while controlling for the number of days of fever before treatment. *P* values < .05 were considered statistically significant.

RESULTS

During the study period, 227 children diagnosed with and treated for KD were identified. We excluded two patients (0.8%) because the KD diagnosis was subsequently clearly rejected by the attending physicians, five patients (2.0%) because no CA measurement was available in our database during the first 3 weeks of follow-up, and 22 patients (8.7%) because no serial follow-up CA measurement was available 2 weeks after diagnosis. The remaining 197 patients were included in the final analyses.

There were 66 patients (33.5%) in the definite CA dilatation category. Of them, 53 (26.9%) and 11 (5.9%) had LMCA *Z* scores > 2.5 and > 5.0, respectively, and 37 (18.8%) and 11 (5.6%) had RCA *Z* scores > 2.5 and > 5.0, respectively. Among patients without definite CA dilatation, occult CA dilatation, as described in the "Methods" section, was detected in 63 (32.0%). The remaining 68 patients (34.5%) had normal CA dimensions. Table 1 details the demographic characteristics as well as CA *Z*-score summaries according to their dilatation categories. Patients with definite CA dilatation were younger ($P = .006$) and were slightly more likely to have incomplete KD criteria, although not statistically significantly. The median number of days of fever before the first dose of IVIG was 6 days (IQR, 5–7 days) for both the normal and occult dilatation categories and 7 days (IQR, 5–8 days) for the definite dilatation category. Compared with the patients in the normal category, the median number of days of fever before the first dose of IVIG was similar in patients in the occult dilatation category ($P = .423$) but significantly higher in patients in the definite dilatation category ($P = .013$). Forty-eight patients (23.9%) had persistent fever after