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Patterns of Carotid Intima–Media Thickness Progression in Kawasaki Patients: A Crystal Ball for Long-Term Vascular Health?

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Kawasaki disease (KD) is an acute vasculitis of unknown etiology that predominantly affects infants and young children. It manifests with fever, rash, enanthem, conjunctival injection, extremity changes, cervical adenopathy, and laboratory test results reflecting intense systemic inflammation.[1] If not treated, 1 in 5 children develop coronary artery aneurysms (CAAs). Administration of high-dose intravenous immunoglobulin and aspirin has been found to reduce the rate of CAAs by 5-fold (from 25% to 5%).[2,3] The goal of therapy in the acute phase of KD is to reduce inflammation in the coronary artery wall and to prevent coronary artery thrombosis.

Patients who develop giant aneurysms suffer the greatest morbidity and mortality. Although the risk of myocardial infarction from coronary artery thrombosis is greatest in the first 2 years after the acute illness, coronary artery stenosis and occlusion progress over years.[4,5] Information regarding coronary artery histology in KD patients is based primarily on autopsies from patients who died as a result of complications from the vasculitis, and this limits our understanding to only the most severe forms.[4] A review of autopsies from KD patients revealed that the arterial pathology includes necrotizing arteritis, subacute or chronic vasculitis, and luminal myofibroblastic proliferation.[4] The acute arteritis is predominantly characterized by neutrophilic infiltrate that can lead to necrosis in the vessel wall. Subacute vasculitis begins weeks after the onset of fever, can still be detected months to years later, and is closely associated with luminal myofibroblastic profileration. Luminal myofibroblastic proliferation is associated with the subacute process that occurs months to years after disease onset and can result in luminal narrowing, which can lead to cardiac ischemia.[4]

In affected patients, CAAs evolve over time, increasing in size during the first few months after the onset of illness and then regressing over the next 2 years to near-normal lumen diameter. Despite the return to normal internal lumen diameter that is seen in small and moderate CAAs, studies have shown late myointimal thickening of the arterial wall with impaired coronary vascular reactivity and coronary flow reserve in these patients.[6–8]

In the current era, the majority of children treated with intravenous immunoglobulin in the acute phase of illness never develop coronary artery abnormalities. Some studies have raised concerns, even in this "always normal" group. Myocardial blood flow and coronary flow reserve were reported to be diminished in a study,[9] and some studies performed in Asia have suggested impaired endothelial function[10] and increased arterial stiffness in these patients.[11] Studies in North America, however, have not detected long-term changes in vascular function of KD patients with no history of coronary artery aneursyms.[12,13]

Several noninvasive vascular assessment modalities that serve as surrogate markers of cardiovascular risk have been used to investigate the vascular health of KD patients. Flow-mediated dilation and pulse amplitude testing have been used to measure endothelial dysfunction. Both modalities are based on the concept of reactive hyperemia caused by increased shear stress that results in endothelial release of nitric oxide and correlates with coronary endothelial function.[14,15] An alternative noninvasive method is measurement of arterial stiffness by pulsed-wave analysis or arterial tonometry, as an indicator of increased cardiovascular disease risk.[16] Another modality for assessing vascular health is carotid artery ultrasound. Increased carotid intima–medial thickness (cIMT) measured by carotid ultrasound has been shown to reliably represent the presence of atherosclerosis.[17]

This issue of *Journal of the American Heart Association* includes a longitudinal cohort study that evaluated the

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long-term impact of history of KD on cardiovascular risk.[18] Dietz et al compared cIMT in 319 patients with a history of KD (median age 8.1 years [range 5–43.3 years] at the first cIMT measurement) and 150 control patients who consisted primarily of siblings of the patients (n=130, median age 12.5 years [range 7–31.1 years]). In only 148 of the 319 KD patients, >1 cIMT measurement was performed over a 15-year period; however, by creating a multilevel, repeated-measures, linear mixed-effects model, the authors were able to use all cIMT measurements to create a large study group.

Of the 319 participants with a history of KD, the majority (241, 75.5%) had a worst-ever coronary artery *z* score of 2.5. The remaining group consisted of 51 patients (16.0%) who had CAAs with *z* scores of 2.5 to 10 and 27 patients (8.5%) with giant aneurysms with *z* scores ≥10 and/or diameters of ≥8 mm. The authors, appropriately, adjusted for sex, body mass index, age, and blood pressure in their analysis model. The investigators reported high reproducibility of cIMT measurements in their laboratory; however, because different machines were used during the course of the study, the investigators incorporated a correction factor in their analysis.

The investigators reported that mean cIMT was increased in KD patients compared with controls (0.375 mm [95% CI 0.372–0.378 mm] versus 0.363 mm [95% CI 0.358–0.368 mm]; $P=0<0.001$).[18] When comparing the different subgroups based on CAA status, mean cIMT was increased across all subgroups compared with controls (0.373, 0.374, 0.381, and 0.363 mm in patients with no CAAs, in patients with CAAs with *z* scores 2.5 to 10, in patients with giant aneurysms, and in controls, respectively).

The model for the longitudinal cIMT data analysis over time showed that all patients with a history of KD started with a higher cIMT (intercept +0.0145 mm [95% CI 0.0042–0.0248 mm; $P=0.006$] at age 5 compared with controls). There was no difference in increase per age-year (−0.0004 mm [95% CI −0.0014 to 0.0007 mm; $P=0.490$] increase per year compared with controls).[18] In further subgroup analyses, compared with controls, patients with no CAAs started with a significantly higher cIMT at age 5 years (+0.0193 mm [95% CI 0.0089–0.0297 mm; $P<0.001$]), but this difference decreased per year (−0.0014 mm per year [95% CI −0.0025 to −0.0003 mm; $P=0.012$]). There was no significant difference between controls and patients with small to medium CAAs, either in cIMT at age 5 years or in cIMT progression per year. Compared with controls, patients with giant CAAs had higher but nonsignificant cIMT levels at age 5 years and a trend toward increased cIMT progression per year (0.0013 mm per year [95% CI −0.0000 to 0.0027 mm; $P=0.058$]).

Within the KD groups, when comparing patients with no CAA and patients with small to medium and giant CAAs, both groups had a comparable intercept at age 5 years, but the latter group had significantly increased progression (0.0015 mm per year [95% CI 0.0001–0.0030 mm; $P=0.038$] and 0.0027 mm per year [95% CI 0.0015–0.0039 mm; $P<0.001$], respectively). The authors also analyzed the data including only the measurements of patients with follow-up data. This analysis showed a result similar to the analyses including all patients.

This study is the first longitudinal cIMT study in KD, demonstrating a gradual increase in cIMT in KD patients with giant aneurysms and showing that patients without history of CAAs demonstrated normalization of cIMT with time, despite an initial increase in cIMT compared with controls. These findings are similar to those of the cross-sectional study by Dietz et al, who observed increased cIMT in all patients with CAAs, whereas in patients with no CAAs, increased cIMT was apparent only at a young age, suggesting similar regression of cIMT with time.[19] In a similar cross-sectional study by Selamet Tierney et al, there was no significant difference in cIMT in KD patients with no CAAs and control patients.[12] These conflicting results could be due to the fact that the patients in the latter study were older, with a mean age of 16.7 years, and thus further from KD onset (median of 11.6 years). The increased cIMT at younger age in patients with no history of CAAs is most likely caused by subsiding inflammation.

Another important finding of the study is that KD patients with giant CAAs had an increased rate of cIMT progression compared with the other KD patients. This finding aligns with several studies published in this population and documenting abnormal vascular health in this subgroup of KD patients. The cIMT is a well-established surrogate marker of atherosclerosis and predictor of cardiovascular events.[17] Increased rate of cIMT progression has been associated with increased incidence of stroke in adult patients who were free from cardiovascular events,[20] and in young adults, it has been associated with cardiovascular risk factors in childhood.[21]

Although it is tempting to suggest that the increased cIMT found in KD patients represents an increased risk of cardiovascular disease, in reality, this inference must be made with caution because of the different vascular pathophysiology that occurs in KD and that differs from traditional atherosclerosis. Despite the fact that the term “atherosclerosis” is loosely applied to vascular lesions found late after KD, autopsy evidence does not support this use. Autopsy reports in KD patients rarely mention lipid-laden macrophages and cholesterol crystals, which are the hallmarks of atherosclerosis.[22] Suzuki et al examined patients who died 3 to 12 years after KD and found active remodeling of the aneurysms with intimal proliferation and neoangiogenesis, but there was no evidence of atherosclerosis.[23] This highlights the importance of prospective tracking of deaths in KD cases and correlation of histopathology with coronary artery findings during the acute illness and with lifetime cardiovascular events to better risk-stratify the KD population.

This eloquent work by Dietz et al adds to the body of literature suggesting that KD patients who never had CAAs do not have higher cardiovascular risk profiles compared with the non-KD population in the long term. Perhaps the use of multiple noninvasive imaging modalities over time in this patient population would provide a clearer picture of vascular health and possibly serve as risk stratification for future cardiovascular events. Until further longitudinal data become available, KD patients should be followed long term and assessed for known cardiovascular risk factors. Clinicians should use the American Heart Association guidelines for cardiovascular risk reduction in high-risk pediatric patients for guidance on treatment, with particular attention paid to the degree of initial coronary artery involvement.[24]

Disclosures

None.

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