Prevalence of Kawasaki Disease in Young Adults With Suspected Myocardial Ischemia

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Background—Up to 25% of patients with untreated Kawasaki disease (KD) and 5% of those treated with intravenous immunoglobulin will develop coronary artery aneurysms. Persistent aneurysms may remain silent until later in life when myocardial ischemia can occur. We sought to determine the prevalence of coronary artery aneurysms suggesting a history of KD among young adults undergoing coronary angiography for evaluation of possible myocardial ischemia.

Methods and Results—We reviewed the medical histories and coronary angiograms of all adults <40 years of age who underwent coronary angiography for evaluation of suspected myocardial ischemia at 4 San Diego hospitals from 2005 to 2009 (n=261). History of KD-compatible illness and cardiac risk factors were obtained by medical record review. Angiograms were independently reviewed for the presence, size, and location of aneurysms and coronary artery disease by 2 cardiologists blinded to the history. Patients were evaluated for number of risk factors, angiographic appearance of their coronary arteries, and known history of KD. Of the 261 young adults who underwent angiography, 16 had coronary aneurysms. After all clinical criteria were assessed, 5.0% had aneurysms definitely (n=4) or presumed (n=9) secondary to KD as the cause of their coronary disease.

Conclusions—Coronary sequelae of KD are present in 5% of young adults evaluated by angiography for myocardial ischemia. Cardiologists should be aware of this special subset of patients who may benefit from medical and invasive management strategies that differ from the strategies used to treat atherosclerotic coronary artery disease. (Circulation. 2012;125:2447-2453.)

Key Words: aneurysm ■ angiography ■ coronary artery disease ■ mucocutaneous lymph node syndrome ■ myocardial ischemia

K

awasaki disease (KD) is an acute, self-limited vasculitis of unknown origin that occurs in young children. It presents as a febrile illness with mucocutaneous changes. Diagnosis depends on recognition of the clinical syndrome because no diagnostic test exists. Although effective treatment reduces the risk of long-term cardiovascular sequelae,1 KD can be difficult to recognize, and many cases go undiagnosed. Approximately 25% of children with untreated KD (and 5% of those treated with intravenous immunoglobulin) will develop coronary aneurysms.2–5 As children with coronary aneurysms due to KD grow older, they are at increased risk for myocardial infarction and other adverse events.3,6 The first presentation in individuals with missed KD may be an ST-segment–elevation myocardial infarction caused by thrombus formation in the aneurysmal segment of the coronary artery.7 Coronary artery damage during acute KD can also lead to calcification and stenotic lesions associated with myointimal proliferation later in life.6,8 However, the true impact of coronary aneurysms and coronary artery damage resulting from KD and their prevalence among young adults presenting with symptoms of cardiac ischemia have not been systematically studied. Therefore, we sought to determine the prevalence of coronary artery aneurysms suggesting a history of KD among young adults undergoing coronary angiography for the evaluation of possible myocardial ischemia.

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Methods

Study Population
All adults <40 years of age who underwent coronary angiography for suspected myocardial ischemia between July 1, 2005, and June 30, 2009, at 4 hospitals in San Diego, CA, were included. Participating hospitals included Sharp Memorial Hospital and San Diego Cardiac Center. The study was approved by the institutional review board at each participating hospital, and participants were informed of the study and provided consent.
Table 1. Clinical and Angiographic Criteria Suggesting Coronary Aneurysms Are Due to Kawasaki Disease

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Subjects Likely to Have KD (n=248)</th>
<th>Subjects Unlikely to Have KD (n=261)</th>
<th>Definite or Presumed KD (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>KD indicates Kawasaki disease.</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2. Characteristics of the Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects (n=261)</th>
<th>Subjects Likely to Have KD (n=248)</th>
<th>Subjects Unlikely to Have KD (n=261)</th>
<th>Definite or Presumed KD (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>35.0±4.6</td>
<td>35.1±4.5</td>
<td>32.9±4.9</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Male, %</td>
<td>72.8</td>
<td>71.4</td>
<td>100</td>
<td></td>
<td>0.02</td>
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<tr>
<td>Race/ethnicity, %</td>
<td>26.8</td>
<td>27.8</td>
<td>7.7</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Black</td>
<td>19.2</td>
<td>19.0</td>
<td>23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>8.4</td>
<td>7.3</td>
<td>30.8</td>
<td></td>
<td></td>
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<tr>
<td>Hispanic</td>
<td>19.2</td>
<td>20.2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8.0</td>
<td>8.5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>18.4</td>
<td>17.2</td>
<td>38.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors, %</td>
<td>28.4</td>
<td>28.3</td>
<td>30.8</td>
<td>0.85</td>
<td></td>
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<tr>
<td>Current smoking</td>
<td>24.9</td>
<td>25.0</td>
<td>23.1</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Family history of early CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21.8</td>
<td>21.8</td>
<td>23.1</td>
<td>0.96</td>
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<tr>
<td>Hypertension</td>
<td>46.0</td>
<td>48.8</td>
<td>30.8</td>
<td>0.23</td>
<td></td>
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<tr>
<td>Hyperlipidemia</td>
<td>46.4</td>
<td>46.4</td>
<td>46.2</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>14.2</td>
<td>13.7</td>
<td>23.1</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>1.1</td>
<td>0</td>
<td>23.1</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

| Laboratory values (mean±SD)                                            |                                    |                                      |                                |       |
| LDL cholesterol, mg/dL                                                 | 112±48                             | 111±46                               | 149±86                            | 0.22  |
| HDL cholesterol, mg/dL                                                 | 38±11                              | 39±11                                | 32±11                              | 0.09  |
| Triglycerides, mg/dL                                                   | 156±132                            | 157±134                              | 137±72                            | 0.66  |

KD indicates Kawasaki disease; CAD, coronary artery disease; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Results

Characteristics of the Study Population

Over the 4-year study period, a total of 268 adults <40 years of age underwent coronary angiography at 1 of the 4 study hospitals and met the study criteria (n=89 at the 2 UC San Diego Health System Hospitals, n=111 at Sharp Hospital, and n=68 at Naval Medical Center San Diego). Of these, charts and angiograms were available for review in 261 (97.4%). Demographics of the study population are shown in Table 2. The mean age of patients was 35 years, and 73% were men. About half of the patients had ≥2 CAD risk factors, and nearly 30% had at least 3 risk factors for CAD. Four patients (1.5%) had a known history of KD.

Angiographic Findings, CAD Risk Factors, and Prior KD

On review of coronary angiograms, 59% had normal coronary arteries at the epicardial level, 39% had stenosis of at least 50%, and 6% (n=16) had coronary artery aneurysms. One individual had a coronary artery anomaly (anomalous takeoff of the left circumflex coronary artery).

Compared with patients with normal coronary arteries, the 16 patients with aneurysms had a similar prevalence of CAD risk factors (mean number of risk factors, 1.9±1.1 in the aneurysm group versus 1.7±1.3 in the normal group; P=NS).
Seven of the 16 patients (44%) with coronary aneurysms had only 1 or no known CAD risk factors compared with 50% of those with normal-sized coronary arteries (P=NS). Among the 16 patients with aneurysms, 5 (31%) had no significant coronary stenosis on angiography.

After all clinical criteria were assessed, 4 of the 16 patients with coronary aneurysms had definite antecedent KD, and 9 had aneurysms presumed to be secondary to KD. Overall, 50% of all patients had definite or presumed KD as the cause of their coronary disease.

Characteristics of the Patients With Coronary Aneurysms

The clinical and angiographic characteristics of the 16 patients with coronary artery aneurysms are shown in Table 3. All 16 patients were men, and 4 (25%) had a known childhood history of KD.

Of the 4 patients with a history of KD, all had coronary aneurysms in ≥2 vessels, and 3 had concomitant coronary artery stenoses of at least 50%. These 3 individuals each had 1 additional CAD risk factor as well: 1 patient had a family history of early CAD; 1 had elevated low-density lipoprotein cholesterol; and the third smoked cigarettes. Patient 1 was a Vietnamese man with a known history of KD at 14 years of age. He had received intravenous immunoglobulin and aspirin on day 13 of illness and had giant aneurysms already present at the time of diagnosis. A computed tomography angiogram at 21 years of age raised concerns for arterial occlusion, and he was taken urgently for coronary angiography, which revealed patent giant saccular aneurysms of all 3 major epicardial vessels with no stenoses. Left ventriculography revealed moderate left ventricular dysfunction with an ejection fraction of 38%, apical dyskinesis, and anterior hypokinesis. Patient 2 was a 29-year-old white man with a history of KD at 3 years of age that was treated with aspirin only because his illness predated the use of intravenous immunoglobulin. He presented with symptoms of heart failure and exertional chest pain; he was found to have 4 sequential giant aneurysms of the left anterior descending coronary artery with stenoses interspaced between them (Figure 1A). There was also a large right coronary artery aneurysm (Figure 1B). This patient underwent attempted percutaneous coronary intervention for a 90% stenosis of the left anterior descending coronary artery. He subsequently developed end-stage ischemic cardiomyopathy with an ejection fraction of 10% and ultimately underwent successful cardiac transplantation. Patient 3, a 34-year-old Cambodian man, presented with an acute ST-segment–elevation myocardial infarction and had a complete thrombotic occlusion of a giant aneurysm in his proximal right coronary artery. He subsequently developed end-stage ischemic cardiomyopathy with an ejection fraction of 10% and ultimately underwent successful cardiac transplantation. Patient 3, a 34-year-old Cambodian man, presented with an acute ST-segment–elevation myocardial infarction and had a complete thrombotic occlusion of a giant aneurysm in his proximal right coronary artery; a history compatible with untreated KD at 6 years of age was elicited retrospectively via parental interview by the interventional cardiologist at the time of angiography. Patient 4 was a 37-year-old Vietnamese man who presented with an acute ST-segment–elevation myocardial infarction with thrombotic occlusion of the right coronary artery. He had giant aneurysms in all 3 major epicardial vessels. Subsequently, a history of KD-compatible illness that went untreated at 6 years of age while he was living in a refugee camp in Thailand was elicited from his parents by the treating team.

In addition to the 4 patients with a known history of KD, there were 3 patients in whom antecedent KD was considered highly probable. Patient 5 was a 33-year-old black man with acute chest pain who was found to have giant aneurysms of his left main coronary artery and all 3 major epicardial vessels (Figure 1C and 1D); there was a large thrombotic occlusion in
his mid left anterior descending coronary artery that measured 12 mm. He had no known history of KD. His only risk factor for CAD was smoking. Patient 6 was a 36-year-old black man with CAD risk factors including hyperlipidemia and hypertension. He presented with chest pain and dyspnea on exertion. Although he had no known history of KD, his angiogram revealed giant aneurysms of the proximal left anterior descending coronary artery and left circumflex vessels. His right coronary artery was ectatic with a smaller aneurysm of the posterolateral branch measuring 5.2 mm. Finally, patient 7 was a 34-year-old diabetic man with a history of hypertension who presented with chest pain and was found to have giant proximal aneurysms of his left coronary system. Angiography revealed an 8-mm left main coronary artery, an aneurysmal, calcified left circumflex vessel that was occluded, and a proximal stenosis of the left anterior descending coronary artery followed by a 15-mm aneurysm. His proximal right coronary artery had a smaller aneurysm measuring 5.5 mm.

In 6 other patients with coronary aneurysms, antecedent KD was considered possible (Figure 2A). These patients tended to have a higher prevalence of CAD risk factors (mean, 2.0±1.1 versus 1.1±0.7 risk factors per person; P=0.11) compared with the patients known or considered to have a history of KD. The mean aneurysm size, although still large, was smaller in this group (6.8±0.7 versus 9.9±2.8 mm; P=0.03), and the aneurysms were less likely to be limited to only the proximal vessels even though most aneurysms included the proximal vessels.

The 3 patients with coronary aneurysms who were deemed unlikely to have KD as a causative factor (Figure 2B and 2C) had an even higher prevalence of CAD risk factors (mean,
3.3±0.6 per person) and smaller mean aneurysm size (5.9±0.9 mm). Two of the 3 patients had at least 50% narrowing of a coronary vessel.

**Discussion**

KD was first described in Japanese children by Tomisaku Kawasaki in 1967,\textsuperscript{10} with the first English language publication in 1974.\textsuperscript{11} Since that time, careful epidemiological studies in Japan have documented increasing disease incidence.\textsuperscript{12,13} The increasing incidence of KD has also been noted in the United States, but it is difficult to distinguish between increased case ascertainment and a true increase in the number of affected children.\textsuperscript{14–16} Reports of missed KD in young adults began to emerge in the 1980s after Kawasaki’s original publication, but no systematic study of such patients has been published.\textsuperscript{2,3} Without a diagnostic test, retrospective diagnosis of missed KD is largely a diagnosis of exclusion.

In the present study, we found that ≈5% of young adults who undergo coronary angiography to evaluate symptoms for myocardial ischemia may have KD as the underlying cause. Furthermore, all 4 patients with a known history of KD had significant aneurysms and a constellation of findings that make it highly probable that their symptoms were due to antecedent KD. Angiographic findings that make antecedent KD likely include proximal aneurysms often with calcification,\textsuperscript{17} followed by an angiographically normal distal segment.\textsuperscript{6} Because a history of KD is unknown in many young adults with coronary aneurysms, recent guidelines have recommended that such patients be diagnosed as having sequelae of KD if other diseases causing secondary aneurysms (eg, collagen vascular disease) are excluded.\textsuperscript{18} Clinical characteristics that make antecedent KD the likely cause, in addition to a history suggestive of prior KD, include a paucity of traditional cardiac risk factors, a younger age, and an ethnicity known to be at higher risk for KD (Asian or black). Interestingly, smoking has been noted as a prominent additional risk factor among young adults with a history of KD who present with myocardial infarction.\textsuperscript{7}

To the best of our knowledge, this is the first study to systematically evaluate a population of young adults undergoing coronary angiography to estimate the prevalence of KD as a potential etiology. Previously, Kato et al\textsuperscript{2} surveyed adult cardiologists in Japan and retrospectively identified 130 patients 20 to 63 years of age with angiographic and clinical findings suggestive of KD. Although a definite history of KD could be elicited in only 2 patients, on the basis of their review of the data, the authors concluded that all 130 patients likely had KD as the cause of their cardiovascular abnormalities. It should be noted that because KD often occurs in infancy or early childhood, the patient would not have a personal memory of the illness, which could be obtained only through parental interview.

Our finding that 5% of all young adults being evaluated for ischemia may have KD as a cause of their symptoms has

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**Figure 2.** Representative images from coronary angiograms of patients with aneurysms considered possibly caused by Kawasaki disease (KD; A) and unlikely to be a result of KD (B and C).

A, Left coronary arteries of patient 10 with possible antecedent KD showing an aneurysm of the proximal diagonal branch of the left anterior descending (LAD) artery.

B, Angiogram of patient 14, considered unlikely to have antecedent KD, showing proximally dilated left main and LAD arteries with mid-LAD occlusion and diffuse stenoses in the left circumflex and obtuse marginal arteries.

C, Angiogram of patient 14, considered unlikely to have antecedent KD, showing a diffusely aneurysmal right coronary artery with focal distal stenoses.
important implications for adult cardiologists. The pathology of coronary lesions in patients with a history of KD is very different from the pathology of typical coronary atherosclerosis, so optimal treatment of each is distinct.19 Although typical atherosclerosis is characterized by lipid-laden macrophages, extracellular lipid droplets, and cholesterol crystals, these features are absent in coronary lesions after KD.20 Acutely, KD vasculopathy begins with endothelial cell swelling and subendothelial edema, followed by an intense inflammatory process leading to regions of myointimal proliferation with focal destruction of the internal elastic lamina, medial smooth muscle cell necrosis, and aneurysm formation.21,22 Over time, myointimal proliferation leads to fibrous scar formation, often with calcification.19,22

Although optimal therapy of young adults with acute coronary syndromes secondary to KD has not been established, consensus guidelines exist, and the divergent pathology strongly suggests that optimal treatment of KD vasculopathy differs in several key ways from treatment of typical atherosclerosis.18,23

Acutely, patients with KD who present with myocardial infarction often have a significant thrombus burden in their aneurysmal segments. In the setting of a large thrombus burden, the true diameter of the aneurysmal segment may not be fully appreciated, and intravascular ultrasound is warranted to prevent undersizing of stents. Because some vessels may be heavily calcified, percutaneous transluminal angioplasty may be complicated by the need for very high balloon filling pressures, leading to neoaneurysm formation.24 Rotational atherectomy is the interventional procedure of choice for heavily calcified, stenotic lesions that are not amenable to percutaneous transluminal angioplasty.6,25 In subacute settings, coronary computed tomography angiography may help as a noninvasive means of identifying the presence and size of aneurysms, as well as the presence of thrombus, calcifications, and stenoses. Long-term therapy with systemic anticoagulation, often in addition to antiplatelet agents, is frequently indicated for patients with large coronary aneurysms and represents another area where treatment differs from that of typical atherosclerosis.18,26–28

Understandably, most adult cardiologists have little to no experience with treating the complications of KD vasculopathy. KD was not described in the United States until the mid-1970s.29,30 Consequently, only in the past 10 to 20 years have KD patients begun to reach young adulthood and come to the attention of adult cardiologists. As more children with a history of KD reach adulthood, adult cardiologists are likely to see increasing numbers of patients with acute and subacute presentations caused by coronary sequelae of KD. It has been estimated that there are currently >24,000 young adults in the United States with a history of KD, including >8000 with a history of coronary artery abnormalities; this number is expected to grow by 1400 individuals each year.6 Thus, increased awareness of the cardiovascular sequelae of KD and their accompanying distinct treatment challenges is more important now than ever before.

Strengths and Limitations
This study has several strengths. The 4 hospitals in this study included academic, private, and military institutions and thus served a diverse population likely to be representative of the population as a whole. In addition, because inclusion criteria were broad and exclusion criteria were very narrow, this study provides an estimate not only of the number of potential cases of cardiac ischemia resulting from KD but also of the denominator (ie, the total number of young adults undergoing evaluation for cardiac ischemia), thereby allowing us to provide a better sense of the magnitude and frequency of this presentation. Our study also has several limitations. San Diego has a relatively high Asian population, which could increase the prevalence of KD compared with other regions. However, there is also a relatively low percentage of blacks in San Diego, another group with increased propensity to develop KD. Results in other regions could vary, depending on the particular ethnic and racial composition of the population. In addition, the determination of whether the coronary aneurysms and cardiac symptoms in the 16 patients were due to KD was somewhat subjective. However, it was based on known epidemiological, clinical, and angiographic correlates of KD.2,3,7 In addition, our determinations were made in accordance with current guidelines on diagnosing and managing the cardiovascular sequelae of KD, which recommend that young adults with coronary aneurysms be diagnosed as having sequelae of KD in the absence of other known causes of aneurysms.18 Further studies are needed to confirm our findings.

Conclusions
Coronary sequelae resulting from KD are responsible for a small but important percentage of young adults who present with myocardial ischemia. Cardiologists should be aware of this special subset of patients who may benefit from medical and invasive management strategies that differ from those used to treat atherosclerotic CAD.

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Disclosures
None.

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