Coronary Artery Dilation Among Patients Presenting With Systemic-Onset Juvenile Idiopathic Arthritis

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ABSTRACT. Objective. To evaluate coronary artery diameters among patients presenting with systemic-onset juvenile idiopathic arthritis (SoJIA).

Methods. Fifty cases of SoJIA were reviewed. At the time of initial presentation with fever, 12 patients had echocardiograms that included a complete evaluation of the coronary arteries. A single reviewer measured the diameters of the left main, proximal left anterior descending, and proximal right coronary arteries. Body surface area-adjusted z scores were calculated with respect to a normative population.

Results. Coronary artery dilation (z score: >2) was observed for 5 of the 12 patients with SoJIA who had echocardiograms performed at the time of presentation with fever. No patient developed a coronary artery aneurysm, and all of the coronary artery z scores normalized within 4 months. Only 2 of the 5 patients with coronary artery z scores of >2 fulfilled the clinical criteria for Kawasaki disease, the most commonly recognized cause of coronary artery dilation among children.

Conclusions. Children presenting with SoJIA may have coronary artery dilation similar to that observed for children with Kawasaki disease. These data suggest that the presence of coronary artery dilation on initial echocardiograms for patients with fever does not exclude the diagnosis of SoJIA. Pediatrics 2005;116:e89–e93. URL: www.pediatrics.org/cgi/10.1542/peds.2004-2190; juvenile rheumatoid arthritis, Still's disease, Kawasaki disease, fever.

ABBREVIATIONS. IVIG, intravenously administered immunoglobulin; KD, Kawasaki disease; SoJIA, systemic-onset juvenile idiopathic arthritis.

Systemic-onset juvenile idiopathic (or rheumatoid/chronic) arthritis (SoJIA) (Still’s disease) is characterized by hectic daily fevers and arthritis. These symptoms may be accompanied by evanescent rashes, lymph node enlargement, hepatomegaly, splenomegaly, or serositis. The disease is associated with elevation of inflammatory indices and circulating levels of proinflammatory cytokines, especially interleukin-6. Aggressive immunosuppressive therapy is often required to achieve disease control. Reported cardiac complications of SoJIA include pericarditis, pericardial effusion, myocarditis, and rarely endocarditis.

Diagnosis of SoJIA is often challenging, especially before children have had symptoms for 6 weeks (as required by International League of Associations for Rheumatology criteria for SoJIA and American College of Rheumatology criteria for systemic-onset juvenile rheumatoid arthritis) or 3 months (as required by European League Against Rheumatism criteria for systemic-onset juvenile chronic arthritis). Infectious diseases and other inflammatory conditions, including childhood vasculitides, may mimic SoJIA. Children with early SoJIA are often treated for Kawasaki disease (KD) when it cannot be excluded by the tenth day of fever and when caregivers think that presumptive therapy of a child who may have KD is necessary. This is more likely to occur when children have other symptoms common to both KD and SoJIA, such as rash, cervical lymphadenopathy, or extremity swelling. Although mucosal changes and isolated cervical lymphadenopathy are more typical of KD, these factors alone may not distinguish KD from SoJIA adequately.

In an attempt to differentiate KD and SoJIA, clinicians often rely on ophthalmologic evidence of uveitis or echocardiographic evidence of coronary artery dilation. Either finding would typically favor the diagnosis of KD, although the incidence of coronary artery dilation in SoJIA is not known. In fact, we observed dilation of the coronary arteries in several patients who were diagnosed eventually as having SoJIA. On the basis of this observation, we evaluated retrospectively the dimensions of the coronary arteries among patients during the initial febrile episodes leading to the diagnosis of SoJIA.

METHODS

We reviewed the medical records of the 50 patients with SoJIA who were treated in the outpatient rheumatology clinic at Children’s Hospital Boston in 2002–2003. Nineteen of these 50 patients had prior echocardiograms. Echocardiograms for 7 of the 19 patients were limited and did not include images sufficient for measurement of the coronary arteries; 6 were obtained for patients

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with previously diagnosed SoJIA, to evaluate possible pericarditis or endocarditis, and 1 was obtained at the time of presentation with fever of unknown origin, to evaluate possible endocarditis. Therefore, 12 of the 19 patients had echocardiograms obtained at the time of their initial febrile presentation that included coronary artery imaging adequate for measurement of the diameters of the left main, proximal left anterior descending, and/or proximal right coronary arteries. These 12 echocardiograms were evaluated more thoroughly, with review of all echocardiograms except for those for patient 1 by a single pediatric echocardiographer (J.C.L.) who was blinded to the original measurements. The studies for patient 1 were not reviewed because they had been reviewed previously, to reach a consensus regarding the coronary artery dimensions, by multiple pediatric cardiologists, including other investigators in this study (S.N.W. and J.W.N.)

Measurements of the internal lumen diameters of the coronary arteries were made by using previously described methods.11 These diameters were compared with measurements for a large sample of normal subjects with body surface area-adjusted z scores. A z score is defined as the number of SDs a measurement lies from the mean for the normal subjects; a z score of >2 indicates that a measurement lies >2 SDs above the mean. Following standard practice, coronary arteries with dimensions >2 SDs above the mean (ie, z scores of >2) were defined as abnormally dilated.11 Our review of the patients’ medical records and echocardiograms was approved by the institutional review board of Children’s Hospital Boston.

RESULTS

Review of the 12 echocardiograms allowed measurement of the coronary artery dimensions for all 3 coronary arteries for 8 patients and for 2 of the 3 coronary arteries for the remaining 4 patients, leading to a total of 32 vessels. The coronary artery z scores for these 12 patients with SoJIA are depicted in Fig 1. Our main finding was that, at the time of initial febrile presentation, 5 patients with SoJIA had ≥1 coronary artery z score of >2 and 2 patients had 2 vessels with z scores of >2.

Table 1 summarizes the clinical and laboratory features at the time of the initial echocardiogram for the 12 patients who were diagnosed ultimately as having SoJIA. Clinical features suggestive of KD tended to occur more commonly among patients with SoJIA with coronary artery z scores of >2, but only 2 of those 5 patients fulfilled KD clinical criteria.

The 5 patients with SoJIA with coronary artery z scores of >2 are described in greater detail in Table 2, with particular attention to features of their presentations that were clinically similar to features of KD. Three patients with SoJIA (including the 2 meeting KD criteria) had a left anterior descending or right coronary artery z score of ≥2.5; 1 of those patients had a right coronary artery z score of ≥3. The coronary artery dilations normalized within 4 months after disease onset, and no patient developed a coronary artery aneurysm. Arthritis was present for 3 of those 5 patients at the time of presentation with fever, and arthritis developed within 1 month after disease onset for the other 2 patients. All 5 of the patients were treated with corticosteroids early in the disease course, for either presumed intravenously administered immunoglobulin (IVIG)-resistant KD (patients 1–4) or presumed SoJIA (patient 5). The corticosteroids were tapered subsequently and discontinued for 4 of the 5 patients, with the addition of other immunomodulatory medications.

DISCUSSION

Both KD and SoJIA should be considered when a child with prolonged fever, rash, and cervical lymphadenopathy is evaluated. In view of our findings for these 5 children and the frequent occurrence of pericarditis in SoJIA and coronary arteritis in KD, echocardiograms often should be included in the evaluation of children for whom these diagnoses are being considered. Documentation of coronary artery dilatation typically would favor the diagnosis of KD. As we have demonstrated, however, similar changes in coronary artery dimensions may occur among children presenting with SoJIA. With this small sample, we were not able to identify any echocardiographic variables that would distinguish patients with acute KD from patients with early SoJIA.

Although arthritis may occur in the acute febrile or convalescent phase of KD, our patients had more persistent signs of systemic inflammation than are usually seen in KD. Furthermore, our patients required aggressive, prolonged, immunosuppressive therapy. In contrast, arthritis during the convalescent phase of KD is typically self-limited and may be controlled with short courses of nonsteroidal anti-inflammatory drugs.

In the absence of pathognomonic physical examination or laboratory findings, clinical criteria are used to establish diagnoses of both SoJIA and KD.1,9 Four of the 5 patients we report with coronary artery

Fig 1. Coronary artery z scores for 12 patients presenting with SoJIA. Values are reported for the left main coronary artery (LMCA), left anterior descending artery (LAD), and right coronary artery (RCA). Circles represent z scores for individual patients, and squares represent the mean value for each vessel (with 95% confidence intervals). The P values comparing these means with 0, the mean z score for normal subjects, are as follows: left main coronary artery, P = .046; left anterior descending artery, P = .007; right coronary artery, P = .067. The z scores correspond to the number of SDs from the expected population mean of 0.
terleukin-6, occurs in both KD and SoJIA. For...

- **Indication for echocardiogram, n (%)**
  - Possible KD: 4 (80) vs 3 (43)
  - Fever of unknown origin: 1 (20) vs 2 (29)
  - Suspected SoJIA: 0 (0) vs 1 (14)
  - Possible acute rheumatic fever: 0 (0) vs 1 (14)

- **Clinical criteria for KD, n (%)**
  - Fever for ≥4 d: 5 (100) vs 7 (100)
  - Rash: 5 (100) vs 6 (86)
  - Unilateral cervical lymph node of ≥1.5 cm: 4 (80) vs 2 (29)
  - Extremity changes: 3 (60) vs 1 (14)
  - Bilateral conjunctival injection: 2 (40) vs 1 (14)
  - Oral changes: 2 (40) vs 1 (14)
  - Fulfilled 5 of 6 KD clinical criteria: 2 (40) vs 1 (14)
  - Treated for KD: 4 (80) vs 1 (14)

- **Clinical characteristics of SoJIA**
  - Duration of fever, d, median (range): 8 (8–19) vs 12 (8–50)
  - Arthritis, n (%): 3 (60) vs 6 (86)
  - Serositis, n (%): 0 (0) vs 1 (14)
  - Generalized lymphadenopathy, n (%): 1 (20) vs 2 (29)
  - Hepatomegaly or splenomegaly, n (%): 2 (40) vs 1 (14)

- **Laboratory parameters, median (range)**
  - White blood cell count, 10⁹ cells per L: 14.2 (10.7–18.7) vs 17.4 (10.7–39.2)
  - Hematocrit, %: 29.0 (24.4–31.9) vs 29.6 (27–35.9)
  - Platelet count, 10⁹ platelets per L: 688 (171–837) vs 506 (324–538)
  - Erythrocyte sedimentation rate, mm/h: 119 (71–176) vs 102 (44–120)

*Coronary Artery z Scores of >2 vs Coronary Artery z Scores of ≤2*

z scores of >2 were treated for KD. Patients 1 and 2 fulfilled KD diagnostic criteria, whereas patients 3 and 4 did not. The simplest explanation for multiple diagnoses among these children is that they had SoJIA but their symptoms could not be distinguished from those of KD early in the disease course. Indeed, many patients treated for KD do not fulfill the diagnostic criteria and are considered to have “incomplete” KD, particularly if coronary artery abnormalities are demonstrated echocardiographically. Although it is possible that some of our patients had both KD and SoJIA, it is statistically unlikely that we would encounter 5 children with the simultaneous onset of both KD and SoJIA at a single institution in a period of 3 years, because both conditions have annual incidence rates of ~10 cases per 100,000.

Another possibility is that KD may trigger or evolve into SoJIA. These 2 systemic inflammatory disorders could share common triggering agents, susceptibility factors, or immunopathogenic pathways. Elevation of circulating levels of inflammatory cytokines, including tumor necrosis factor-α and interleukin-6, occurs in both KD and SoJIA. For most patients, KD is a self-limiting illness. It may be hypothesized that, for individuals with immunologic and/or genetic risk factors for the development of SoJIA, KD may trigger a self-perpetuating inflammatory cascade through abnormal immunoregulatory mechanisms. This hypothesis is particularly intriguing in view of the tendency of our patients with SoJIA with coronary artery dilation to present with features suggesting KD (Tables 1 and 2). It should be noted, however, that we have not observed coronary artery aneurysms typical of KD for any of our patients with SoJIA.

The design of our study does introduce important limitations. First and most importantly, in our retrospective study, several patients with SoJIA did not have prior echocardiograms. It is likely that echocardiograms were obtained more commonly for patients with SoJIA presenting with clinical features suggestive of KD, potentially leading to an increased likelihood of detecting dilated coronary arteries. A prospective study to estimate coronary artery z scores for all patients presenting with SoJIA would be necessary to eliminate this type of ascertainment bias. Second, the normative data used to determine coronary artery z scores for all patients presenting with SoJIA were obtained for an afebrile population of children. It is possible that prolonged fever alone causes transient coronary artery dilation. Despite these limitations, we have documented that coronary artery dilation can be observed among febrile children shortly before the diagnosis of SoJIA is established. Until more is understood about the cause and pathogenesis of both KD and SoJIA, diagnosis and therapy will continue to rely on clinical criteria and acumen.

Our findings have implications for the treatment of patients presenting with features of KD and SoJIA. If a patient meets the criteria for KD, then appropriate therapy with IVIG and acetylsalicylic acid (aspirin) should be instituted. However, our report suggests that rare patients in this category may have or may develop SoJIA. Therefore, careful follow-up monitoring is necessary to document the resolution...
<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation, y</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
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<tr>
<td>Presenting symptoms and signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever for ≥4 d</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rash</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Unilateral cervical lymph node of ≥1.5 cm</td>
<td>X</td>
<td>X</td>
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<td>Extremity changes</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Bilateral conjunctival injection</td>
<td>X</td>
<td>By report</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oral changes</td>
<td>X</td>
<td></td>
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<tr>
<td>KD clinical criteria met (maximum: 6)</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Treated for KD</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>No. of doses of IVIG (2 g/kg per dose)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Time between onset of fever and onset of arthritis, wk*</td>
<td>2</td>
<td>Simultaneous</td>
<td>Simultaneous</td>
<td>4</td>
<td>Simultaneous</td>
</tr>
<tr>
<td>Coronary artery dimensions and z scores† (initial; final)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main coronary artery, mm</td>
<td>3.7; 2.7</td>
<td>3.4; 2.9</td>
<td>2.3; 2.3</td>
<td>2.3; 2.4</td>
<td>4.0; 4.0</td>
</tr>
<tr>
<td>Left main coronary artery, z score</td>
<td>3.19; 0.5</td>
<td>1.39; 0.01</td>
<td>0.1; 0.1</td>
<td>0.48; 0.75</td>
<td>1.75; 1.5</td>
</tr>
<tr>
<td>Left anterior descending artery, mm</td>
<td>2.5; 1.9</td>
<td>2.7; 2.6</td>
<td>2.2; 1.7</td>
<td>2.2; 1.8</td>
<td>3.4; 3.4</td>
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<tr>
<td>Left anterior descending artery, z score</td>
<td>2.47; −0.32</td>
<td>1.32; 0.77</td>
<td>1.63; −0.46</td>
<td>2.2; 0.56</td>
<td>2.18; 1.71</td>
</tr>
<tr>
<td>Right coronary artery, mm</td>
<td>NM; 1.8</td>
<td>0.35; 0.30</td>
<td>2.6; 2.4</td>
<td>2.3; 2.0</td>
<td>32; 2.2</td>
</tr>
<tr>
<td>Right coronary artery, z score</td>
<td>NM; 0.18</td>
<td>3.18; 1.63</td>
<td>2.53; 1.8</td>
<td>2.08; 1.13</td>
<td>1.44; −1.04</td>
</tr>
<tr>
<td>Time to normalization of z scores‡</td>
<td>4 mo</td>
<td>5 d</td>
<td>5 d</td>
<td>1 mo</td>
<td>1 mo</td>
</tr>
<tr>
<td>Duration of SoJIA</td>
<td>16 mo</td>
<td>4 y</td>
<td>10 mo</td>
<td>2 y</td>
<td>18 mo</td>
</tr>
<tr>
<td>Current medications</td>
<td>Methotrexate, infliximab</td>
<td>Methotrexate, naproxen</td>
<td>Methotrexate, prednisolone, etanercept, thalidomide, methylprednisolone</td>
<td>Methotrexate, hydroxychloroquine</td>
<td></td>
</tr>
</tbody>
</table>

* X indicates that the symptom or sign was present; NM, not measured.
† X indicates that the symptom or sign was present; NM, not measured.
‡ The z scores were adjusted for body surface area. Identical vessel measurements result in different z scores based on differences in body surface area between patients or for an individual patient (eg, attributable to weight gain for patient 5).
† Time between the initial echocardiogram demonstrating coronary artery dilation and the first echocardiogram with normal coronary artery z scores.
of symptoms after treatment for KD. Persistence of fever with the development of frank arthritis should alert physicians to the possibility of SoJIA. The finding of coronary artery dilation should not dissuade physicians from the diagnosis of SoJIA. Rather, our data suggest that transient coronary artery dilation may occur early in the course of SoJIA.

Should all patients with a systemic inflammatory syndrome and coronary artery dilation be treated with IVIG regardless of whether KD diagnostic criteria are met? Should patients with SoJIA and coronary artery dilation be treated with IVIG? Providing answers for these interrelated questions is difficult. One of our patients with SoJIA (patient 5) with a coronary artery z score of >2 did not meet the criteria for KD and was not treated with IVIG or aspirin. Her coronary artery dimensions normalized after treatment with orally administered corticosteroids. Furthermore, none of our patients with SoJIA developed coronary artery aneurysms, and all of the coronary artery z scores normalized. Although these findings are reassuring, the number of patients with SoJIA with documented coronary artery dilation was small, and 4 of 5 of our patients were treated with IVIG. Given the risks associated with not treating patients with KD, we continue to recommend IVIG therapy for patients with significant coronary artery dilation and systemic inflammation when an experienced clinician believes that the child could have KD. It seems that coronary artery dilation supports a diagnosis of KD but is not specific for the condition.

Our findings also suggest that vigilance is necessary during the long-term treatment of patients with SoJIA. It is possible and even likely that the coronary artery dilation we observed results from vascular inflammation. The link between vascular inflammation and atherosclerosis is highlighted by the increased risk of coronary artery disease and myocardial infarction among adults with rheumatoid arthritis or systemic lupus erythematosus. Furthermore, longer disease duration seems to increase the risk of coronary artery disease among these patients, whereas aggressive disease control decreases it. By extension, it is conceivable that children with SoJIA are at increased risk for coronary artery disease as adults, perhaps because of coronary inflammation that is usually subclinical at presentation. The relative risk of premature atherosclerotic coronary artery disease among adults with a history of SoJIA or KD is unknown. One case report linked fatal postpartum coronary thrombosis to localized coronary artery dilation for a 27-year-old woman with a nearly lifelong history of SoJIA. Our report opens important avenues to explore the pathogenesis, management, and consequences of coronary artery dilation among patients with SoJIA.

REFERENCES

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