Recognition and management of Kawasaki disease

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Abstract

Kawasaki disease is an acute systemic vasculitis of unknown cause that primarily affects children under 5 years of age. It was first described in Japan in 1967 by Dr. Tomisaku Kawasaki and colleagues.1 Since then, it has been reported worldwide and is now recognized as the leading cause of acquired heart disease in children in the developed world, surpassing acute rheumatic fever in the United States.2,3

The last published review of the Canadian experience with Kawasaki disease was by Rowe and Rose in 1985.4 Despite the tremendous progress in treatment and the resulting dramatic decrease in the rate of cardiac complications since then, the cause of Kawasaki disease remains unknown. The clinical presentation, self-limited course, seasonality, epidemics and patient age group suggest an infectious cause activating an immune response in genetically predisposed people.5,6 However, no single agent has been consistently associated with the disease.

The diagnosis of Kawasaki disease is based on the same clinical features originally used to describe the disease more than 30 years ago.1 Unfortunately, these clinical findings are nonspecific and are commonly found in many pediatric infectious and immunologic diseases. Further complicating the diagnosis is the fact that these clinical features may be absent or may evolve over many days after fever onset. Hence, Kawasaki disease presents a diagnostic challenge, and a high index of suspicion is required for early diagnosis and initiation of treatment.

The purpose of this article is to describe the epidemiology, clinical features, management and outcomes of Kawasaki disease and to increase awareness of it across Canada.

Epidemiology

Studies in the United States have reported annual incidence rates of 6.5 to 15.5 per 100 000 among children less than 5 years of age, a male–female ratio of 1.5:1 and seasonal peaks in winter and spring.2,3,9–11 Worldwide, the highest incidence rate remains in Japan, where nationwide surveys have reported annual rates of about 100 per 100 000 among children in that age group, a male–female ratio of 1.4:1 and no consistent seasonal trends.12,13

In Ontario the mean annual incidence rates of Kawasaki disease among chil-
Clinical features and diagnosis

Recommendations on when to suspect Kawasaki disease and refer patients are outlined in Table 1. The diagnostic criteria proposed by the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease are presented in Table 2. In our survey of Ontario cases, all patients had fever, the median duration of which was 6.5 (range 1–29) days; in 51 cases the fever lasted less than 5 days as a result of early treatment or atypical presentation. The most common clinical features were oral mucosal changes (in 94% of cases) (Fig. 2) and conjunctivitis (in 92%) (Fig. 3); the next most common features were rash (in 90%), changes in the extremities (in 77%) and cervical lymphadenopathy (in 64%) (Fig. 4). Because these clinical features are nonspecific, other diseases with similar presentations and features should be ruled out. The differential diagnosis of Kawasaki disease is presented in Table 3.

Other less common clinical findings may include arthralgia, arthritis, vomiting, diarrhea, abdominal pain, hydrops of the gallbladder, hepatitis, urethritis, irritability, aseptic meningitis and sterile pyuria. Cardiac abnormalities in the acute phase may include tachycardia out of proportion to the fever, electrocardiographic changes (e.g., decreased R-wave voltage, changes in the ST and T waves, presence of at least 4 of the following principal features:"

Table 1: Indications for diagnosis and referral of patients suspected of having Kawasaki disease

- Kawasaki disease should be considered in a child with persistent and unabating fever and
- no focus of infection, or
- no response to antimicrobial treatment, or
- other clinical or laboratory features of Kawasaki disease

If a child is suspected of having had acute Kawasaki disease in retrospect (i.e., 5 of 6 principal clinical features), refer to a pediatric cardiologist for cardiac assessment and follow-up.

Table 2: Diagnostic criteria for Kawasaki disease

| Fever of at least 5 days’ duration (high, spiking, not responsive to antimicrobial or antipyretic agents) |
| Presence of at least 4 of the following principal clinical features:* |
| • Polymorphous exanthem (involving face, trunk, extremities, perineal region) |
| • Bilateral conjunctivitis (nonexudative, bulbar more than palpebral or tarsal) (Fig. 3) |
| • Changes in the lips and oral cavity (dry cracked lips, “strawberry tongue,” erythema of oropharynx) (Fig. 2) |
| • Changes in extremities (erythema of palms and soles, edema of hands and feet, followed 1–3 weeks later by desquamation of fingers, toes and, in infants, perineal region) |
| • Cervical lymphadenopathy (> 1.5 cm in diameter, usually firm, slightly tender) (Fig. 4) |

Exclusion of other diseases with similar findings

*A typical Kawasaki disease may be diagnosed in patients with fever who have fewer than 4 of the principal features if they have coronary artery changes noted on 2-dimensional echocardiography.

Fig. 1: Age and sex distribution of cases of Kawasaki disease in Ontario diagnosed between Jan. 1, 1995, and Dec. 31, 1997.
and prolonged PR or QT intervals), myocarditis occasionally leading to congestive heart failure, pericardial effusion and mitral regurgitation. Laboratory findings may include neutrophilia, anemia, thrombocytosis, elevated erythrocyte sedimentation rate, elevated serum transaminase levels, hypoalbuminemia, positive C-reactive protein test result and an elevated serum $\alpha_1$-antitrypsin level.5,6

The diagnosis of typical Kawasaki disease is established when a child has a fever and 4 or 5 of the 5 other principal clinical features (Table 2). Patients with fever but fewer than 4 of the remaining principal features can be said to have atypical disease if they have coronary artery abnormalities detected by echocardiography or, less commonly, by coronary angiography. Patients with fever, fewer than 4 other features and no coronary artery abnormalities can be said to have incomplete Kawasaki disease if it continues to be suspected as the diagnosis. Incomplete disease may reflect atypical disease that does not progress to form coronary artery aneurysms, successfully treated atypical disease or an erroneous diagnosis.

From our survey of Ontario cases we found that the youngest and the oldest groups of children were less likely than those in the middle age groups to present with typical disease. In our study population, 31% of children less than 1 year old and 31% of those more than 9 years had atypical or incomplete Kawasaki disease, as compared with 16% of those who were 1 to 4 years of age, 19% of those 5 to 9 years. Hence, an early diagnosis of Kawasaki disease may be difficult to make because of nonspecific clinical features that may only evolve over time, and the presence of atypical and incomplete cases.

**Coronary artery aneurysms**

The prevalence of coronary artery aneurysms in children with Kawasaki disease has substantially decreased since the initiation of intravenous gamma globulin (IVGG) treatment. Coronary artery aneurysms develop in 18% to 23% of children who do not receive such treatment, as compared with 4% to 8% of those who receive it within 10 days of fever onset.13 Maximum coronary artery involvement is usually within the first 6 to 8 weeks from fever on-
set. In our Ontario survey 24% (92/382) of patients had coronary artery ectasia (size of coronary artery larger than normal for age), 8% (31/382) had non-giant coronary artery aneurysms (internal diameter > 4 mm and < 8 mm), and less than 1% (3/382) had giant coronary artery aneurysms (internal diameter ≥ 8 mm) on their initial echocardiogram.

**Risk factors**

Factors associated with an increased risk of coronary artery aneurysms include male sex, age less than 1 year and fever lasting more than 10 days. In our Ontario survey, patients in the youngest and oldest groups had the highest risk of coronary artery aneurysms, with 15% of patients less than 1 year and 17% of those 10 to 14 years having aneurysms, as compared with 8% of children 1 to 4 years of age and 6% of those 5 to 9 years. There was a trend toward a greater rate of aneurysms among patients who did not receive IVGG treatment than among those who did (18% v. 8%, p = 0.08). Among the patients who received IVGG treatment, the rate of aneurysms was significantly lower if the treatment was given within 10 days of fever onset than after 10 days (6% v. 27%, p < 0.001). Multiple logistic regression analysis revealed that no IVGG treatment within 10 days of fever onset was an independent risk factor for coronary artery aneurysms. After controlling for treatment, the risk of aneurysms remained highest in the youngest age group (less than 1 year of age).

These findings are consistent with a study in British Co-

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**Table 4: Treatment of acute Kawasaki disease**

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<tr>
<th>Intravenous gamma globulin (IVGG)</th>
<th>2 g/kg as single infusion over 12 hours; should be given within 10 days of onset of fever</th>
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<tr>
<td>Acetylsalicylic acid (ASA)</td>
<td>80–100 mg/kg per day, divided into 4 doses, until patient is afebrile, then 3–5 mg/kg every day for 6–8 weeks†</td>
</tr>
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Evidence-based guidelines do not exist for the management of patients in the following situations:
- Patients who are afebrile at time of presentation
- IVGG usually not recommended; give low-dose ASA
- Patients with persistent or recurrent fever after initial dose of IVGG
  - May repeat IVGG dose or give intravenous corticosteroid therapy
- Patients with evidence of myocarditis (i.e., diminished ventricular function, ventricular arrhythmias)
  - Supportive therapy, may give intravenous corticosteroid therapy or repeat IVGG

†If varicella or influenza develops, ASA therapy should be stopped to reduce the risk of Reye’s syndrome.

**Table 5: Long-term management of patients with Kawasaki disease by degree of maximal coronary artery involvement**

<table>
<thead>
<tr>
<th>No coronary artery changes</th>
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<tbody>
<tr>
<td>- Give low-dose ASA therapy for the first 6–8 weeks, then no medications or activity restrictions</td>
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<tr>
<td>- Follow-up with echocardiography at end of first year, then no further follow-up with echocardiography is recommended</td>
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<tr>
<th>Transient coronary artery dilatation (ectasia)</th>
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<tr>
<td>- Give low-dose ASA therapy for the first 6–8 weeks, then no medications or activity restrictions</td>
</tr>
<tr>
<td>- Follow-up with echocardiography at end of first year, then no further follow-up with echocardiography is recommended</td>
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<tr>
<td>- Further follow-up is discretionary</td>
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<tr>
<th>Small- to medium-sized (&gt; 4 mm and ≤ 8 mm in diameter) solitary coronary artery aneurysms</th>
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<tr>
<td>- Continue low-dose ASA therapy at least until abnormalities resolve</td>
</tr>
<tr>
<td>- There are no activity restrictions for children &lt; 10 years of age; for those over 10 years of age, activity recommendations are guided by the results of annual exercise stress testing (preferably with nuclear medicine myocardial perfusion scanning or stress echocardiography)</td>
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<tr>
<td>- Perform annual follow-up with echocardiography and electrocardiography</td>
</tr>
<tr>
<td>- Perform coronary angiography if stress testing suggests cardiac ischemia (stenoses)</td>
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<tr>
<th>One or more giant aneurysms (≥ 8 mm in diameter), or multiple small- to medium-sized aneurysms, without obstruction</th>
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<tr>
<td>- Prescribe long-term low-dose ASA therapy with warfarin</td>
</tr>
<tr>
<td>- There are no activity restrictions for children &lt; 10 years of age; for those over 10 years of age, activity recommendations are guided by the results of annual exercise stress testing (preferably with nuclear medicine myocardial perfusion scanning or stress echocardiography)</td>
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*Cardiovascular risk reduction recommendations are made to all patients, and include institution of a low fat and low cholesterol prudent diet, exercise prescription with maintenance of an ideal body weight, and avoidance of tobacco use and exposure.
lumbia, which also demonstrated that age less than 1 year, age 9 years and older, and a delay in diagnosis were important risk factors for coronary artery aneurysms.\(^\text{14}\)

**Natural history**

Most coronary artery aneurysms regress within a year after the acute phase of Kawasaki disease. In our study 8% (31/382) of patients had coronary artery aneurysms on their initial echocardiogram, but only 3% (13/375) had aneurysms on follow-up echocardiograms at 12 months after diagnosis. In a comprehensive follow-up study involving 594 consecutive children 10 to 21 years after Kawasaki disease was diagnosed, Kato and colleagues,\(^\text{16}\) using coronary angiography, reported that 55% of patients with aneurysms had regression, most within 2 years of diagnosis, and 19% had coronary artery stenoses. Akagi and associates\(^\text{17}\) found that regression of aneurysms was significantly related to the reduced severity of coronary artery lesions, initial treatment with IVGG and male sex. Burns and colleagues\(^\text{18}\) conducted a literature review and identified 74 reported cases of adult coronary artery disease attributed to childhood Kawasaki disease; they found that the mean age at onset of symptoms of cardiac ischemia was 25 (range 12 to 39) years, with symptoms precipitated by exercise in 82% of these patients.

Patients in whom coronary artery aneurysms regress may be at increased risk of atherosclerotic lesions, because of the disturbance and proliferation of the intima during aneurysm development and regression.\(^\text{19}\) This is further supported by Dhillon and associates,\(^\text{20}\) who found signs of endothelial dysfunction, a precursor to atherosclerosis, in people 5 to 17 years after Kawasaki disease had been diagnosed. Hence, although the rate of coronary artery aneurysms has been reduced with prompt treatment, and about 50% of aneurysms regress within 1 to 2 years after acute onset of Kawasaki disease, the long-term sequelae concerning the risk of coronary artery disease remain unclear.

**Treatment**

**Initial management**

The goal of initial management is to reduce inflammation and thus reduce the risk of coronary artery abnormalities. The recommended treatment regimen is presented in Table 4. A multicentre randomized controlled trial in the United States demonstrated that IVGG and acetylsalicylic acid (ASA) given within 10 days of fever onset resulted in a significantly lower rate of coronary artery abnormalities than ASA alone.\(^\text{14}\) Subsequently, high-dose IVGG therapy (single dose of 2 g/kg) has been shown to be more effective than low-dose IVGG therapy (400 mg/kg per day for 4 days).\(^\text{21}\) A Canadian study had also found that, compared with low-dose IVGG therapy, high-dose therapy consumes fewer resources and results in a better clinical outcome.\(^\text{22}\)

Nonetheless, in our survey of Ontario cases 7% (29/400) of patients did not receive IVGG, and 6% (22/371) of those who received it were given it after 10 days of fever onset. Almost all patients (97%) received at least low-dose ASA therapy. The absence or delay of IVGG treatment was significantly related to the patient’s age at diagnosis (in 11% of children less than 1 year of age, 11% of those 1 to 4 years, 17% of those 5 to 9 years and 38% of children 10 to 14 years \(p = 0.02\)). The difference among age groups may reflect a delay in diagnosis in the older group, as was also noted by Momenah and colleagues.\(^\text{11}\) Hence, Kawasaki disease should be considered in the differential diagnosis of fever in the older as well as the younger child.

**Long-term management**

The recommendations on long-term management that appear in Table 5 are based on those from the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease.\(^\text{23}\) These recommendations are based on risk stratification and depend on the relative risk of myocardial ischemia.

**Conclusion**

Kawasaki disease has become the leading cause of acquired heart disease in children in the developed world. However, the cause remains unknown. The incidence rate of Kawasaki disease in Canada appears steady, at about 13 per 100 000 among children less than 5 years of age. However, this rate may be an underestimation, because it does not include cases diagnosed outside of hospital and those missed because of the difficulties in clinical diagnosis arising from the lack of specific diagnostic tests, nonspecific clinical features, self-limited clinical course, and atypical and incomplete presentations. The rate of cardiac complications can be substantially reduced with prompt diagnosis and early treatment with IVGG. However, delays in diagnosis and treatment continue, particularly in older children. Increased diagnostic suspicion and prompt referral may reduce the risk of cardiac complications.

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**References**


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