Recognition and management of Kawasaki disease

Review

Synthèse

Ra K. Han,* Brian Sinclair,‡ Alice Newman,* Earl D. Silverman,† Gregory W. Taylor,§ Peter Walsh,§ Brian W. McCrindle*

From the Divisions of *Cardiology and †Rheumatology, Department of Pediatrics, University of Toronto and The Hospital for Sick Children, Toronto, Ont.; ‡the Division of Cardiology, Department of Pediatrics, University of Ottawa and Children's Hospital of Eastern Ontario, Ottawa, Ont.; and §the Bureau of Cardio-Respiratory Diseases and Diabetes, Laboratory Centres for Disease Control, Health Canada, Ottawa, Ont.

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Abstract

KAWASAKI DISEASE IS THE LEADING CAUSE of acquired heart disease in children in the developed world, with coronary artery aneurysms occurring in up to 25% of untreated cases. The mean annual incidence of Kawasaki disease across Canada is about 13 per 100 000 children less than 5 years of age, based on hospital discharge data from 1990 to 1995. The cause remains unknown, and the diagnosis is based on the same clinical criteria used to describe the disease over 30 years ago. However, nonspecific clinical features, evolving presentations and atypical or incomplete presentations make early diagnosis and timely treatment difficult. Delays in diagnosis and treatment, which occur more frequently in older children, are associated with an increased risk of coronary artery aneurysms. Hence, high diagnostic suspicion and prompt referral are required to reduce the rate of cardiac complications.

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.[1,5] 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-

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dren less than 5 years of age from 1990/91 to 1995/96 (based on hospital discharge abstract data from the Canadian Institute for Health Information and Statistics Canada) were 14.6 and 14.7 per 100 000 respectively. The mean rates across Canada among children less than 5 years of age were 13.8 per 100 000 from the CIHI database (excluding Quebec) and 13.8 per 100 000 from the Statistics Canada database. There were minor geographic variations across the country, with the lowest rate in Prince Edward Island and the highest in Newfoundland (with wide confidence limits). The overall annual incidence rates were steady, with no epidemics noted between 1990/91 and 1995/96.

A previous survey of Ontario hospitals reported a mean annual incidence rate of 11.3 per 100 000 among children under 5 years of age for 1989–1990.[7] A subsequent study, based on data from The Hospital for Sick Children in Toronto and the Hôpital Sainte-Justine in Montreal, estimated a mean annual incidence rate of 7.7 per 100 000 in Ontario and 7.5 per 100 000 in Quebec for 1990–1995.[8]

We conducted a mail and telephone survey of all hospitals (excluding chronic care and mental health facilities) and pediatric cardiologists in Ontario. We asked them to identify all cases of Kawasaki disease (International Classification of Diseases, 9th revision, clinical modification, code 446.1) diagnosed between Jan. 1, 1995, and Dec. 31, 1997, and to complete a standardized data-collection form regarding each case. All 178 eligible hospitals and all pediatric cardiologists responded, describing a total of 430 cases. Fig. 1 depicts the distribution of these cases by age and sex. Most of the cases occurred before the age of 5 years. Using the 1996 Canada Census data for Ontario, we estimated that the mean annual incidence rate per 100 000 was 14.5 among children less than 5 years of age, 4.1 among those 5 to 9 years, 0.6 among those 10 to 14 years and 0.2 among adolescents 15 to 18 years of age. We also noted that the male–female ratio was 1.8:1 and that there were 2 seasonal peaks in incidence, the larger one in the winter and the smaller peak in the summer.

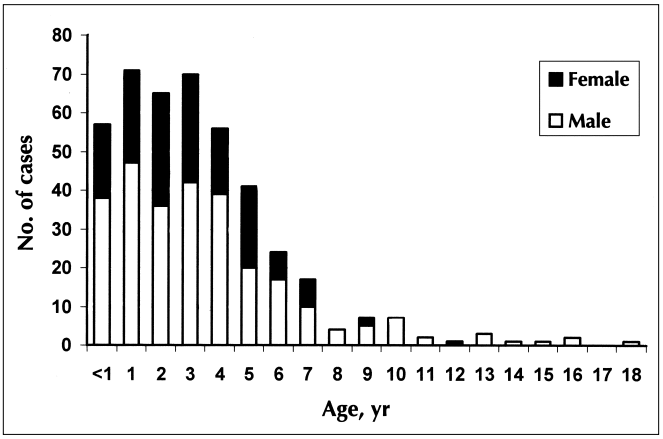

Fig. 1: Age and sex distribution of cases of Kawasaki disease in Ontario diagnosed between Jan. 1, 1995, and Dec. 31, 1997.

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.[5] 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.[5,6]

Other less common clinical findings may include arthralgia, arthritis, vomiting, diarrhea, abdominal pain, hydrops of the gallbladder, hepatitis, urethritis, irritability, aseptic meningitis and sterile pyruria. 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,

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

*Atypical 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. 2: Red tongue and prominent papillae ("strawberry tongue") in patient with Kawasaki disease.

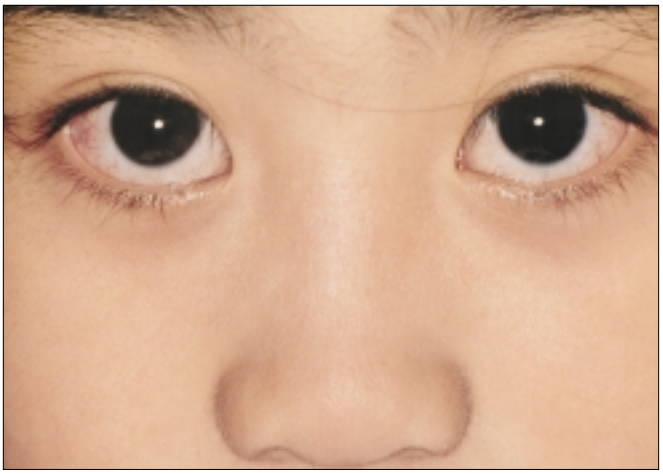

Fig. 3: Conjunctivitis without mucopurulent discharge in patient with Kawasaki disease.

Fig. 4: Prominent submandibular swelling on right side indicative of cervical lymphadenopathy (often unilateral) and fissured red lips in patient with Kawasaki disease.

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 α_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-

Table 3: Differential diagnosis of Kawasaki disease

Infectious diseases	Rocky Mountain spotted fever
Measles	*Yersinia pseudotuberculosis* infection
Scarlet fever	**Allergic and rheumatic diseases**
Epstein–Barr virus infection	Drug reaction
Adenovirus infection	Steven–Johnson syndrome
Enterovirus infection	Juvenile rheumatoid arthritis
Human parvovirus B19 infection	Polyarteritis nodosa
Staphylococcal scalded skin syndrome	Reiter's syndrome
Toxic shock syndrome	**Toxic conditions**
Leptospirosis	Mercury poisoning

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.

Table 4: Treatment of acute Kawasaki disease

Intravenous gamma globulin (IVGG)
2 g/kg as single infusion over 12 hours; should be given within 10 days of onset of fever

Acetylsalicylic acid (ASA)
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†

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.
†Discontinue ASA therapy 6–8 weeks after onset of illness if no coronary artery aneurysms are observed on follow-up echocardiography.

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.[5] 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-

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

No coronary artery changes

- Give low-dose ASA therapy for the first 6–8 weeks, then no medications or activity restrictions
- Follow-up with echocardiography at end of first year, then no further follow-up with echocardiography is recommended

Transient coronary artery dilatation (ectasia)

- Give low-dose ASA therapy for the first 6–8 weeks, then no medications or activity restrictions
- Follow-up with echocardiography at end of first year, then no further follow-up with echocardiography is recommended
- Further follow-up is discretionary

Small- to medium-sized (> 4 mm and ≤ 8 mm in diameter) solitary coronary artery aneurysms

- Continue low-dose ASA therapy at least until abnormalities resolve
- There are no activity restrictions for children < 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)
- Perform annual follow-up with echocardiography and electrocardiography
- Perform coronary angiography if stress testing suggests cardiac ischemia (stenoses)

One or more giant aneurysms (≥ 8 mm in diameter), or multiple small- to medium-sized aneurysms, without obstruction

- Prescribe long-term low-dose ASA therapy with warfarin
- There are no activity restrictions for children < 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; pharmacologic stress testing may be recommended for children < 10 years of age), although strenuous activities are discouraged. Non-contact recreational activities are encouraged
- Perform annual follow-up with echocardiography and electrocardiography; additional electrocardiography at 6-month intervals is discretionary
- Perform coronary angiography if stress testing suggests cardiac ischemia (stenoses); angiography may be performed as baseline at 3 to 12 months after acute illness, and electively thereafter in certain circumstances

Coronary artery obstruction (stenosis or occlusion)

- Prescribe long-term low-dose ASA therapy with warfarin; consider use of calcium-channel blockers to reduce myocardial oxygen consumption
- Advise patient to avoid contact sports, isometrics and weight training; recommendations for non-contact recreational activities are guided by the results of stress testing with nuclear medicine myocardial perfusion scanning or stress echocardiography
- Perform follow-up echocardiography and electrocardiography at 6-month intervals; perform ambulatory electrocardiography and stress testing annually
- Perform angiography to assess suitability for intervention (catheter-based or surgical); repeat angiography if results of follow-up stress testing or symptoms suggest cardiac ischemia

*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.[15]

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,[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[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[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.[19] This is further supported by Dhillon and associates,[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.[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).[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.[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.[15] 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.[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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Competing interests: None declared.

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Reprint requests to: *Dr. Brian W. McCrindle, Division of Cardiology, The Hospital for Sick Children, 555 University Ave., Toronto ON M5G 1X8; fax 416 813-7547; brian.mccrindle@sickkids.on.ca*