



Kawasaki disease

Principal investigators

Rosie Scuccimarri, MD, Assistant Professor, Department of Paediatrics, McGill University, Paediatric Rheumatologist, Montreal Children's Hospital, C505-2300 Tupper St., Montréal QC H3H 1P3; tel.: 514-412-4268; fax: 514-412-4365; rosie.scuccimarri@muhc.mcgill.ca

Rae Yeung, MD, PhD, Professor of Paediatrics, Immunology and Medical Sciences, University of Toronto, Paediatric Rheumatologist and Senior Scientist, The Hospital for Sick Children, 555 University Ave., Toronto ON M5G 1X8; tel.: 416-813-8964; fax: 416-813-4989; rae.yeung@sickkids.ca

Co-investigators

David Cabral, MD, University of British Columbia, BC Children's Hospital
Nagib Dahdah, MD, Université de Montréal, CHU Sainte-Justine
Derek G. Human, BM, BCh, University of British Columbia, BC Children's Hospital
Heather A. Hume, MD, Université de Montréal, CHU Sainte-Justine
Bianca Lang, MD, Dalhousie University, IWK Health Centre
Brian McCrindle, MD, MPH, University of Toronto, The Hospital for Sick Children
Sarah Schwartz, MD, University of Toronto, The Hospital for Sick Children

Background

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology. It is currently the leading cause of acquired heart disease in North American children. Although it can affect children of all ages, it occurs mainly in those less than five years of age. This disease is more common among the Japanese and Asian population but can affect children of all ethnicities. The major complication of KD is the development of coronary artery abnormalities (CAA) such as dilatations or aneurysms. If untreated, up to 25% of patients will develop CAA, and mortality may be as high as 2%.

KD is diagnosed based on the presence of characteristic clinical findings. To establish the diagnosis, four out of five criteria must be present, in addition to fever for five days. This is not always easy to make since there is no diagnostic test, which may lead to a delay in the initiation of treatment. Compounding this difficulty is the fact that even some patients who do not fulfill criteria (incomplete KD) can go on to develop CAA. Therefore, physicians need to have a high index of suspicion for this disease. The goal of treatment is to prevent CAA from developing. Early treatment with intravenous immunoglobulin (IVIG) has been shown to significantly reduce the incidence of this complication.

IVIG is felt to be a safe and effective treatment in KD. However, over the last five years or so, the paediatric rheumatology community across Canada has noted a significant number of cases of hemolytic anemia associated with this treatment in children with KD. The Canadian Blood Services also noted an increase in reporting of this complication. It is thought that this is dose-dependent and patients with KD may be at higher risk given that they receive large doses (2 g/kg) at diagnosis, and in approximately 15% of patients, a second dose is required. The incidence of this complication is unknown and more information is required regarding this phenomenon



to better inform how patients with KD are managed, as well as to assist physicians and families during the informed consent process.

Although common in Japan, the incidence of KD in North America is approximately 10 times less than that of Japan. Data on the epidemiology of KD in Canada is limited. Four surveys were conducted in Ontario from 1995 to 2006. An annual incidence of 26.2 per 100,000 children less than five years of age was reported. The Ontario incidence is likely higher than the rest of Canada (except for British Columbia), given a higher population of Asians living in this province. To date, there has been no nationwide epidemiologic survey on KD in Canada, but KD has been reported from across the country. Not only are the disease and potential treatment complications of significant public health concern, but the results of this study will provide much needed evidence for treatment decisions, evidence-based changes to management strategies, and advocacy for access to better therapies.

Methods

To maximize case capture, national surveillance of KD will be conducted using two parallel methods:

- 1) Through the established methodology of the CPSP, over 2,500 clinically active paediatricians and paediatric subspecialists will be actively surveyed monthly for new cases of KD. Respondents who identify a case will be asked to complete a detailed questionnaire for each case.
- 2) Paediatric rheumatologists across Canada already involved in nationwide surveillance and research programs as members of CAPRI (Canadian Alliance of Paediatric Rheumatology Investigators) will act as local site champions on behalf of the research team and help answer questions that may arise at their local sites regarding this project. Respondents who identify a case will be asked to complete identical detailed questionnaires by mail, or by web-based reporting. If respondents are members of the CPSP, they will be asked to report via the CPSP program.

Case definition

Report any new patient presenting before the age of 18 years with a definite or presumed diagnosis of KD:

- 1) **Complete Kawasaki disease (KD)**, defined as fever persisting for five* days or more
AND the presence of **at least four** of the following clinical criteria:
 - Changes in the peripheral extremities
 - erythema of the palms and/or soles; edema of the hands and/or feet; periungual desquamation
 - Polymorphous rash
 - Bilateral bulbar conjunctival injection without exudate
 - Changes in the lips and oral cavity
 - erythema and/or cracking of the lips; strawberry tongue; diffuse erythema of the oropharynx
 - Cervical lymphadenopathy: >1.5 cm diameter, usually unilateral

* Presumptive diagnosis and initiation of treatment may be made before the fifth day of fever.
- 2) **Incomplete KD**, defined as fever of five days or more and less than four clinical criteria.



Kawasaki disease (continued)

- 3) **Other KD**, defined as KD not fulfilling criteria for complete or incomplete KD but presumed because of a feature on echocardiogram or follow-up (i.e., periungual desquamation) that has led the treating physician to recommend treatment and/or cardiac follow-up.

Objectives

- 1) Ascertain the incidence of KD in Canada.
- 2) Describe the clinical features and epidemiology, including the ethnic, regional, geographic and seasonal variations, of KD in Canada.
- 3) Ascertain the incidence of cardiac complications in Canadian children and the risk factors associated with the development of these complications.
- 4) Ascertain the incidence of acute complications associated with IVIG treatment, particularly hemolytic anemia, and the associated risk factors.
- 5) Describe variations in the treatment of KD across Canada and explore how these relate to cardiac and treatment-related complications.

Duration

November 2013 to November 2014

Expected number of cases

A total of 500 cases per year is estimated to meet the inclusion criteria.

Ethical approval

Research Ethics Board, The Hospital for Sick Children

Analysis and publication

Annual and final reports will be published in the *CPSP Results* and circulated to all participants. Dissemination of completed study results will be submitted for publication to appropriate peer-reviewed journals and presented at national and international scientific meetings. Results will also be shared via a study website and in partnership with KD Canada, a family support group for families of children with KD.

Bibliography

Berard R, Whittemore B, Scuccimarri R. Hemolytic anemia following intravenous immunoglobulin therapy in patients treated for Kawasaki disease: A report of 4 cases. *Pediatr Rheumatol Online J* 2012;10(1):10.

Lin YT, Manlhiot C, Ching JC, Han RK, Nield LE, Dillenburg R et al. Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. *Pediatr Int* 2010;52(5):699-706.

Luca NJ, Yeung RS. Epidemiology and management of Kawasaki disease. *Drugs* 2012;72(8):1029-38.

Manlhiot C, Christie E, McCrindle BW, Rosenberg H, Chahal N, Yeung RS. Complete and incomplete Kawasaki disease: Two sides of the same coin. *Eur J Pediatr* 2012;171:4:657-62.

Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY et al. Diagnosis, treatment, and long-term management of Kawasaki disease. *Circulation* 2004;110:2747-71.

Scuccimarri R. Kawasaki disease. *Pediatr Clin North Am* 2012;59(2):425-45.