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New insights into cardiovascular disease in patients with Kawasaki disease

Jane C. Burns^a and Tomoyo Matsubara^b

Purpose of review

Kawasaki disease presents many challenges to the diverse group of physicians who care for these patients including infectious disease specialists, rheumatologists, and cardiologists. Here we review some of the progress being made toward improved understanding of disease pathogenesis, treatment, and long-term outcomes.

Recent findings

Epidemiologic studies in different populations documented increasing numbers of cases in countries with high physician awareness of the disease. These data suggest true increases in patient numbers rather than increases because of increased case ascertainment. Adequately powered clinical trials for adjunctive therapies continue to be an unmet need. Long-term consequences of damage to the arterial wall and myocardium are beginning to emerge and systematic, longitudinal observational studies are needed to better define outcomes.

Summary

The unknown cause, lack of a specific diagnostic test, and uncertain future for patients who develop permanent cardiovascular damage all require further study.

Keywords

coronary artery aneurysm, epidemiology, inflammation, infliximab, intravenous immunoglobulin

INTRODUCTION

Kawasaki disease is not going away! Several reports over the last year documented rising incidence in countries where increases in case ascertainment because of increasing physician awareness are unlikely. In Japan, the country of highest incidence worldwide, analysis of the 2013 and 2014 national surveys revealed an incidence of 308/100 000 children less than 5 years [1^{••}]. A study from Taiwan followed a birth cohort of over 2 million infants and ascertained an incidence of 56/100 000 less than 5 years with an increasing incidence for each year of the study [2^{••}]. The overall cumulative incidence for boys over the first 5 years of life was 3.33/1000. In the United States, investigators used the Kids' Inpatient Database, an administrative database of hospital discharges, to estimate the incidence of Kawasaki disease [3]. In 2012, there were 5033 hospitalizations for Kawasaki disease in the database yielding an incidence of 18/100 000 children less than 5 years. Here we highlight recent insights into the pathogenesis, treatment, and management of coronary artery sequelae of Kawasaki disease [4^{••},5–8] (see Tables 1 and 2).

INSIGHTS INTO DISEASE PATHOGENESIS AND BIOMARKERS

An epidemiologic survey in Canada analyzed questionnaires from approximately 80 Kawasaki disease patients and controls and found an increased likelihood of an antecedent minor illness in the month prior to disease onset in the Kawasaki disease patients [9^{••}]. Variations in Kawasaki disease incidence were correlated to westerly winds carrying increased numbers of fungal particles. The authors propose a model for Kawasaki disease susceptibility that includes host genetics and environmental

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KEY POINTS

- Numbers of Kawasaki disease patients are continuing to increase, especially in Asia.
- Patients with an abnormal initial echocardiogram should receive adjunctive therapy, although the best practice for choice of therapy must await adequately powered, randomized clinical trials.
- The new generation of oral anticoagulants including direct thrombin inhibitors and oral anti-Factor Xa agents should be studied in patients with giant aneurysms as warfarin fails to deliver well-tolerated and effective anticoagulation in this population.
- Autopsy data suggests on-going inflammation in the coronary arteries of patients who died with giant aneurysms and raises questions about the need for better biomarkers and possibly anti-inflammatory therapy for these patients during life.

exposures following priming with an antecedent minor acute infection.

The search continues for diagnostic biomarkers to differentiate acute Kawasaki disease from other rash/fever illnesses in childhood. A mass spectrometry-based proteomic analysis of two Kawasaki disease patients with acute and convalescent serum samples identified lipopolysaccharide-binding protein (LBP), leucine-rich alpha-2-glycoprotein (LRG1), and angiotensinogen as potential biomarkers [10]. Both LBP and LRG1 were elevated in acute Kawasaki disease sera by Western blot analysis and enzyme-linked immunosorbent assays in

approximately 50 Kawasaki disease patients compared with 150 control children with bacterial, viral, or autoimmune diseases. LBP participates in the innate immune response and stimulates release of pro-inflammatory cytokines. LRG1 is associated with fibrosis and blood vessel remodeling. No analysis of the potential utility of these protein as biomarkers using receiver-operator characteristic curves was provided.

MicroRNAs (miRs), small, noncoding RNA molecules that degrade targeted mRNAs, were the subject of several studies. Levels of miR-92a-3p were significantly higher in acute vs. convalescent Kawasaki disease sera and were highest in Kawasaki disease patients who developed coronary artery aneurysms (CAA) [11]. Another study found miR-223 to be elevated in serum of acute Kawasaki disease patients with CAA [12]. However, as these miRs are released from platelets, caution must be exercised in interpreting these results that used serum instead of platelet-poor plasma to avoid the artifact of release of miRs from platelets during clotting.

A study of the coronary arteries from 12 Kawasaki disease patients who died 2–8 weeks after disease onset revealed evidence of on-going antigen presentation and interferon response in the tissues with high levels of allograft inflammatory factor 1 (AIF1), interleukin 18 (IL-18), CD74, CD1c, CD20, Toll-like receptor 7 (TLR-7) and Z-DNA-binding protein 1 (ZBP1) [13]. The authors emphasize the complexity of cross-talk between the innate and adaptive immune systems that persists within the arterial wall in subacute Kawasaki disease.

NEW INSIGHTS INTO TREATMENT

Intravenous immunoglobulin (IVIG) in combination with aspirin has been the mainstay of therapy for acute Kawasaki disease since the mid-1980s. An important new analysis by collaborative epidemiology teams from Japan and the United States has clarified that IVIG should be administered as early in the disease course as possible [14]. This report supersedes an earlier report that suggested that early administration of IVIG was associated with a greater risk of IVIG-resistance. When stratifying for receipt of additional therapies as a surrogate for disease severity, the early administration of IVIG on illness days 1–4 was actually protective [odds ratio (OR) 0.90, 95% confidence interval (CI) 0.8–1.0].

The role of high-dose aspirin (ASA) for acute Kawasaki disease was called into question in two recent studies. Kawasaki disease is essentially the last condition in pediatric medicine for which ASA is used as an anti-inflammatory agent. Its use stems from the original multicenter IVIG clinical trial in

Table 1. Diagnostic criteria for Kawasaki disease

| |
|--|
| Fever of at least 4 days' duration* |
| Presence of at least four of the following five conditions*: |
| Bilateral conjunctival injection |
| Changes in the lips and oral mucosa |
| Dry, red, fissured lips |
| Strawberry tongue |
| Opharyngeal erythema |
| Changes in the extremities |
| Erythema of palms and soles |
| Edema of hands and feet |
| Periungual desquamation |
| Polymorphous rash |
| Cervical lymph node more than 1.5 cm |
| *Diagnosis may be made earlier in course of fever by experienced clinicians. |
| Illness not explained by other known disease processes |

Adapted from the 2017 AHA guidelines [4].

Table 2. Treatment of acute and subacute Kawasaki disease

| Treatment | Dose | Indication and comment |
|---|---|---|
| Intravenous immunoglobulin (IVIG) [5] | 2 g/kg i.v. over 8–10 h | Reduce inflammation by modulating the immune system |
| Aspirin (ASA) | Different centers use high (80–100 mg/kg/day), moderate (30–50 mg/kg/day), or low dose (3–5 mg/kg/day) in combination with IVIG | High–moderate dose ASA used as an anti-inflammatory agent until fever subsides; low dose used as an antiplatelet agent until platelet count less than 450 000 |
| Adjunctive therapies for patients with z score greater than 2.5 on initial echo | | |
| Infliximab [6] | 5–10 mg/kg i.v. over 2 h | Efficacy unproven |
| Methylprednisilone ×2 days, then oral prednisone [7] | 2 mg/kg/day i.v. ×2 days, then orally for 3–5 weeks | Efficacy supported by one RCT |
| Cyclosporine [8] | 5 mg/kg/day orally divided once in 12 h until CRP normalized or 2 weeks, whichever is longer | Efficacy unproven |

Controversies exist over dose of aspirin (ASA) in the acute phase. However, there is consensus on use of antiplatelet dose of ASA after cessation of fever and until the platelet count normalizes. The 2017 AHA guidelines suggest use of adjunctive anti-inflammatory therapy for patients with z score of the left anterior descending (LAD) or right coronary arteries (RCA) greater than 2.5, but choice of therapy remains controversial. Patients with z score at least 10.0 should receive systemic anticoagulation with low-molecular-weight heparin or intravenous heparin transitioning to warfarin.

the United States that compared IVIG with high-dose ASA (80–100 mg/kg/day) to high-dose ASA alone, which was considered the standard of care in the 1980s [15]. A multicenter, retrospective study of over 1200 Kawasaki disease patients over an 11-year period in Canada compared aneurysm rates (z score ≥ 2.5) in patients who received either low-dose ASA (3–5 mg/kg per day) or high-dose ASA (80 mg/kg per day) [16[■]]. No difference was detected in coronary artery outcome between the two dose regimens. Another retrospective study from Israel reached similar conclusions [17].

Debate continues regarding the best choice for adjunctive therapy to treat IVIG-resistant Kawasaki disease patients and to prevent CAA. Wardle *et al.* [18[■]] reported the results of a Cochrane Database analysis. They selected seven randomized trials involving 922 acute Kawasaki disease patients who were treated with various doses of corticosteroids for varying lengths of time. They concluded that moderate quality evidence suggested that corticosteroids can be associated with improved coronary artery outcomes and shorter duration of hospital stay. High-quality data showed reduced time to normalization of laboratory parameters of inflammation (erythrocyte sedimentation rate and C-reactive protein). There were insufficient data available regarding incidence of adverse effects attributable to steroids, mortality and long-term (>1 year) coronary morbidity.

An alternative approach using infliximab to block the pro-inflammatory cytokine, TNF α , was analyzed from the results of a nationwide survey of 274 Japanese institutions [19[■]]. A total of 434 patients with refractory Kawasaki disease received infliximab (5 mg/kg) as second-line, third-line, or

fourth-line treatment. Of these, 83.6% patients became afebrile within 2 days, and the white blood cell count, percentage of neutrophils, and serum CRP levels significantly decreased. In patients without CAAs before infliximab (IFX), 10.3% of patients newly developed CAA after IFX, whereas 24.2% of patients with CAA before IFX showed increased CAA severity. The authors concluded that infliximab was well-tolerated and potentially effective for treatment of IVIG-resistant Kawasaki disease and should be studied in a prospective clinical trial.

The pathophysiology of aneurysm formation includes myofibroblast proliferation and accumulation of these pro-inflammatory cells in the intima and media of the arterial wall. A study by He *et al.* [20[■]] demonstrated a benefit of atorvastatin in reducing myofibroblast transformation of human endothelial cells cultured with sera from Kawasaki disease patients treated with atorvastatin in a phase I/IIa clinical trial.

For patients with giant aneurysms (z score ≥ 10.0), the AHA guidelines recommend systemic anticoagulation with at least one antiplatelet agent. Warfarin has been the mainstay of anticoagulant therapy for these children, although some centers opt for enoxaparin injections. A study from Boston Children's Hospital investigated the safety and efficacy of warfarin for nine Kawasaki disease patients with giant CAA over a 6-year period [21]. Both bleeding and clotting complications were experienced by six of the nine patients and the international normalization ratio was in range only two-thirds of the time. This small study underscores the need for pediatric clinical trials of the newer direct thrombin inhibitors or oral anti-FactorXa agents that are in widespread use for adult patients.

EMBRACING CORONARY ARTERY Z SCORES

A major recent advance is the international adoption of coronary artery z scores as the preferred, quantitative method for the describing deviations from normal for the internal diameter of the coronary arteries normalized for body surface area. The American Heart Association 2017 guidelines endorsed z scores as the classification system that should be used to describe the left anterior descending (LAD) and right coronary arteries (RCA) over time [4²²]. Limitations of this approach were also enumerated and included: anatomic variation in the left main coronary artery making z scores less useful for this vessel; sensitivity of the body surface area calculation to small variations in the measurement of length (height); sensitivity of the z score to small variations in measurement of the internal diameter. Thus, sonographers and cardiologists interpreting the echocardiograms must be vigilant for these potential sources of error.

Not only are z scores a quantitative method to compare changes in arterial dimension in a given patient over time or in response to therapy but also they serve as a predictor of outcomes. In a single center study from the United States, comparing various risk score systems from Japan with baseline echo data, investigators found that a baseline z score of at least 2.0 predicted subsequent aneurysms with a sensitivity of 80% and an excellent negative predictive value of 98% [22²³]. This suggests that clinical trials of interventions to prevent aneurysms should focus on the population of patients with an RCA or LAD z score at least 2.0.

In a departure from tradition, the Japanese also endorsed coronary artery z scores as a useful tool to assess the severity of CAA in relation to subsequent cardiac events [23²⁴]. In their analysis of a multicenter Japanese cohort of 1006 Kawasaki disease patients, the 10-year cardiac event-free rate was 100, 94, and 52% for men with z scores 5, 5–10, and greater than 10, respectively.

LONG-TERM OUTCOMES

Several studies investigated aspects of Kawasaki disease in the late convalescent phase that may have important implications for subsequent cardiovascular health. It has long been appreciated that all Kawasaki disease patients have varying degrees of myocardial inflammation during the acute illness that is usually subclinical. Feature tracking by echocardiography or cardiac MRI (CMRI) can reveal more subtle changes in left ventricular (LV) function that are not apparent using routine methods to assess LV

ejection fraction. In a study of 29 Kawasaki disease patients, a median of 5.8 years out from disease onset, Bratis *et al.* [24] performed feature tracking by CMRI and found lower average longitudinal and circumferential strain at all levels in Kawasaki disease patients regardless of aneurysm status compared with normal controls. Another study examined LV and right ventricular (RV) strain patterns by echocardiography and found reduced strain in all 35 Kawasaki disease patients compared with controls, regardless of coronary artery status [25²⁶].

Further evidence of sequelae from antecedent inflammation was the finding of increased aorta intima thickness and reduced carotid distensibility in a cohort of 65 Kawasaki disease patients at least 2 years out from their initial disease [26]. This finding was largely confined to patients with CAA. It is important to note that there are no data to support any claim that Kawasaki disease patients have increased susceptibility to atherosclerosis compared with the general population and the finding of increased intimal thickening in various vascular beds is often misinterpreted. Similarly, another intriguing observation regarding dilated retinal venules in convalescent Kawasaki disease patients suggests that abnormal endothelial cell function or microvascular disease may be sequelae of Kawasaki disease [27²⁸]. This study of 135 Kawasaki disease patients of Asian or Northern European descent documented larger dimensions in the retinal venules in the Asian descent patients regardless of coronary artery sequelae from their acute Kawasaki disease. Taken together, these studies suggest that we have much to learn about manifestations of Kawasaki disease vasculopathy and the possibility of long-term endothelial cell dysfunction and ongoing vascular inflammation with entirely unknown, if any, clinical consequences.

NEW INSIGHTS INTO THE PATHOPHYSIOLOGY OF CONVALESCENT KAWASAKI DISEASE

Transcript abundance and protein expression was studied in coronary arteries from fatal Kawasaki disease cases in the convalescent phase by reverse transcription polymerase chain reaction, immunohistochemistry and immunofluorescence studies [28²⁹]. Allograft inflammatory factor 1 (AIF1) was highly expressed in stenotic arteries and co-localized with CD68+ macrophages. T lymphocyte and interferon pathway genes were also highly expressed in the arteries. These findings provide evidence of ongoing antigen presentation and interferon response locally in Kawasaki disease arteritis long after the acute phase of the illness.

CONCLUSION

Insights from the recent published literature suggest that the numbers of Kawasaki disease cases are continuing to rise, at least in Asia. Consensus is building that patients with early evidence of coronary artery damage by echocardiogram are candidates for initial adjunctive therapy, but adequately powered, randomized trials are needed to address the best therapeutic approach. Evidence is gathering that there is on-going inflammation in the coronary arteries in patients with giant aneurysms and better functional assessments and imaging for inflammation are needed to understand long-term effects in the myocardium and arterial wall.

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Conflicts of interest

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