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SPECIAL SECTION ON CORONARY ANOMALIES

WILEY Congenital Heart Disease

Kawasaki disease: State of the art

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Abstract

Kawasaki disease is an acute febrile arteritis of childhood that can result in coronary artery aneurysms if untreated in the first 10 and ideally 7 days of illness. Kawasaki disease begins as a necrotizing arteritis with neutrophilic infiltrate, followed by subacute/chronic changes and luminal myofibroblastic proliferation that can cause coronary artery stenosis. Manifestations include the presence of ≥5 days of fever, together with clinical criteria of extremity changes, rash, conjunctivitis, oral changes, and unilateral cervical lymphadenopathy. Echocardiography should be performed at the time of diagnosis, then 1–2 weeks and 4–6 weeks later, with more frequent studies in individuals with coronary artery dilation or persistent fever. Coronary artery dimensions are characterized both as z-scores and absolute measurements, and coronary architecture evolves over time in children who have aneurysms in the first weeks of illness. Systematic follow-up and therapies are tailored to the degree of coronary disease and to coronary ischemia.

KEYWORDS

arteritis, coronary aneurysm, Kawasaki disease, myocardial ischemia

Kawasaki disease KD was first described as "mucocutaneous lymph node syndrome" by a Japanese pediatrician, Dr Tomisako Kawasaki, in 1967.[1] The illness was believed to resolve without intervention, and its association with coronary aneurysms was unknown. In those early days, echocardiographic visualization of coronary arteries had not yet been developed, and there was no known effective therapy. The illness has now been described worldwide, in children of every race and ethnicity. The original diagnostic criteria included fever of >101°F persisting at least 5 days, together with at least 4 of the 5 following criteria: bilateral conjunctival injection; erythema and cracking of lips, strawberry tongue, and erythema of pharynx; erythema and edema of hands and feet with later peeling; a polymorphous exanthema; and cervical lymphadenopathy (>1.5 cm), usually unilateral. In 2004, an American Heart Association Scientific Statement revised the epidemiologic case definition to allow the diagnosis on Day 4 in the presence of complete criteria.[2] In addition, KD could be diagnosed in patients with fever and <4 principal criteria if aneurysms were detected by echocardiography or angiography.

Today, KD strikes ≈5000 US children annually. Indeed, it has surpassed rheumatic fever as the leading cause of acquired heart disease in children in developed countries.[3] Without early treatment with intravenous immunoglobulin (IVIG) treatment, coronary artery aneurysms occur in 1 in 5 children and can result in angina, myocardial infarction, ischemic cardiomyopathy, and sudden death.[2] More than 75% of acute cases are under the age of 5 years, but the disease can occur through adolescence; boys outnumber girls by 1.3–1.5:1. Children of Japanese ancestry have an incidence of 240 per 100 000 children <age 5 years, compared to 17, 11, and 9 per 100 000 children in blacks, Hispanics, and Caucasians, respectively.[4,5] The recurrence rate in Japanese children is 3%.

The etiology of KD remains unknown. Clinical features resemble infectious diseases, such as streptococcal disease, staphylococcal toxic shock syndrome, and atypical measles. Reported epidemiologic risk factors include carpet shampoo, preexisting eczema, humidifier use, residence near a standing body of water, older maternal age, maternal Group B strep colonization, and hospitalization in early infancy for bacteria illness.[6] Scholars debate whether KD could be caused by bacterial superantigens versus viruses, as well as whether KD is due to a single etiology or different etiologic agents with a common final pathway. Intracytoplasmic perinuclear inclusion bodies with the appearance of viral particles have been found in postmortem KD specimens,[7] but a virus has not been identified to date. Tropospheric wind patterns from Central Asia have been associated with KD incidence in Japan, San Diego, and Hawaii;[8] deep sequencing of tropospheric dust has disclosed Candida species. Although KD is not a Mendelian genetic disease, genetic factors appear to predispose both to the disease and to coronary aneurysms. The importance of genetic factors is apparent from differences in risk by race, a 10-fold higher relative risk in siblings,

and emerging recognition of KD in successive generations in Japan. Many manuscripts have described signaling pathways participating in KD pathogenesis and new avenues for treatment.[9] For example, the calcineurin-NFAT (ITPKC) pathway contributes to susceptibility to KD and to aneurysms, suggesting efficacy of calcineurin inhibitors. The contribution of TGFβ and SNPs in TGFβ2, TGFβR2, and SMAD3 to relative risk of coronary aneurysms opens the possibility that statins may be effective. Polymorphisms in FCGR2A (encoding FcγRIIa) contribute to disease susceptibility, a finding consistent with the demonstrated efficacy of IVIG. In the future, genomics research (eg, whole genome sequencing, epigenetics) may disclose many new risk factors for KD and its sequelae.

In recent histologic studies by Orenstein and colleagues,[10] the vasculopathic process in KD has been characterized as acute necrotizing arteritis, with a synchronous, self-limited neutrophilic process of endothelium, progressively destroying the arterial wall from adventitia to intima. In the subacute and chronic phase, inflammatory cells (eg, lymphocytes and macrophages) were found in the adventitia, progressing to the lumen, and causing transition of medial and adventitial SMCs into myofibroblasts. Luminal myofibroblastic proliferation appeared to progress to stenosing luminal lesions.

Among aneurysmal coronary artery segments, approximately half will regress to normal lumen diameter after 2 years; smaller aneurysms are most likely to regress.[11] Even in regressed segments, however, intravascular ultrasound has demonstrated myointimal thickening. Coronary artery stenosis is progressive over years and develops at the inlet and/or outlet of giant in greater than 90% of affected segments in the two decades after illness onset. Fortunately, the development of collateral arteries prevents symptoms in many such patients. In a single center cohort of 70 patients, the survival rate of patients with giant aneurysms was 88% at 20 years.[12] In a larger Japanese survey of outcome of patients with giant aneurysms over 3 decades, survival was 90%, freedom from any coronary intervention was 36%, and freedom from acute myocardial infarction was 74%.[13] Outcomes were worse among those with bilateral compared to unilateral coronary aneurysms. Among patents with at least one myocardial infarction, 30-year survival was 63%, and freedom from ventricular tachycardia by 30 years was only 28.5%.

As in adult atherosclerotic coronary artery disease, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are used to treat patients with ischemic heart disease. In one large Japanese survey, PCI and CABG were similar in the primary composite endpoint of death or q wave myocardial infarction.[14] However, patients treated with PCI had a shorter time to repeat target vessel revascularization, adjusting for sex, age at procedure, and left ventricular ejection fraction. These analyses favored a CABG strategy even for children $<$12 years and those with ischemic changes, although inferences were limited by the retrospective nature of the study. Delineation of the optimal indications and forms of revascularization would benefit from larger prospective data registries.

Debate continues about the need for cardiologic follow-up in patients with always normal coronary arteries. Late clinical manifestations have not been noted in this group despite more than 40 years of follow-up, and the absence of late coronary artery calcification on CT scan is reassuring.[15]

Regardless of coronary status, all patents should have preventive cardiology counseling to minimize risk factors for atherosclerotic coronary disease. Although no single etiologic agent of KD has been found, basic research may expose the critical pathogenic mechanisms to provide better therapies and to identify the vulnerable host. In the future, multicenter trials and registries may allow us to assess the effectiveness of existing and new therapies.

CONFLICT OF INTEREST

Consultant to Bristol-Myers Squibb, Merck, and Daichii Sankyo.

AUTHOR CONTRIBUTIONS

The author contributed in the concept/design, drafting, critical revision and approval of the article.

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