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Review Article

Preventing coronary artery lesions in Kawasaki disease

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ABSTRACT

A form of systemic vasculitis that affects mostly small and medium-sized vessels, Kawasaki disease (KD) is most commonly found in children under the age of 5 years old. Though its etiology is unknown, KD has been the most frequent acquired heart disease in developing countries. Its incidence has increased over recent decades in many centuries, including Japan, Korea, and China. The most severe complications of KD are coronary artery lesions (CAL), including dilation, fistula, aneurysm, arterial remodeling, stenosis, and occlusion. Aneurysm formation has been observed in 20–25% of KD patients that do not receive intravenous immunoglobulin (IVIG) treatment, and in 3–5% that do receive it. Coronary artery dilation has been found in about 30% of KD patients in the acute stage, although mostly in the transient form. Diminishing the occurrence and regression of CAL is a vital part of treating KD. In this review article, I demonstrate the clinical method to prevent CAL formation used at the Kawasaki Disease Center in Taiwan.

Kawasaki disease (KD) is recognized as the most frequent acquired heart disease in children. Dr. Kawasaki et al. first described this acute febrile systemic vasculitis in Japan in 1967 [1]. It mainly affects children under the age of 5 years old, especially those in such Asian countries as Japan, Korea, Taiwan, and China. As a form of systemic vasculitis, KD has been reported to predominantly involve small to medium-sized vessels. The most severe complication or sequela is the formation of coronary artery lesions (CAL), such as myocardial infarction, coronary artery fistula [2], coronary artery dilatation, and coronary artery aneurysm, which may subsequently result in long-term sequelae like stenosis or obstruction and myocardial infarction [3]. The etiology of KD continues to be unknown [4–6], but it has demonstrated an increasing incidence worldwide, particularly in Japan. However, this increase has not been significant in Taiwan [7–10].

KD may be caused by a combination of genetic background (*CD40*, *BLK*, *ITPKC*, *FCGR2A*, *CD40L*, *CASP3* ... etc.) [11–22], infectious agents (bacteria, virus, mycoplasma, etc.) [6,23] and immune response [24,25]. The standard treatment for KD is high-dose aspirin (80–100 mg/kg/day) and high-dose intravenous immunoglobulin (IVIG, 2 g/kg), which have been shown to significantly decrease the rate of coronary artery aneurysms from 20–25% to 3–5% [26,27]. While a single high dose of IVIG has been found to be more effective than four smaller daily doses or two daily doses with the same

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accumulation dosage [5], the effectiveness of IVIG for treating KD is still under investigation. *FCGR2A* may be the answer from genome-wide association study (GWAS) and methylation array results [15,28]. Hypomethylation of CpG sites in the *FCGR2A* promoter region were reported to be related to KD susceptibility and IVIG resistance; mRNA gene expression confirmed such findings. *FCGR2A* is over expressed in the acute stage and then subsides to the same range once controlled, which may indicate the treatment efficacy of IVIG in KD patients, as well as the possible role of purified Fc portion products in future KD treatments [15,28].

While IVIG treatment significantly decreases the occurrence of coronary artery aneurysm formation, about 1/3 of KD patients will still develop coronary artery dilation in the acute stage. In our previous reports, using a serial analysis of coronary artery dilation (n = 341) [29], 35% of KD patients experienced dilatation in the acute stage, 17.2% noted dilatation one month after the onset of the disease, 10.2% still had dilatation two months after the onset of the disease, and 4% had CAL or aneurysm formation for at least one year. Identifying KD during the 5–10 days of disease onset is very important, as is treating KD with a more precise protocol, especially for those children with IVIG resistance, in a high-risk group, or with CAL formation. In this article, I demonstrate the clinical practice of preventing CAL formation adopted by the Kawasaki Disease Center in Taiwan.

How to diagnose typical and atypical Kawasaki disease

Clinical diagnosis criteria (Kuo Mnemonic: 1–2–3–4–5)

The clinical characteristics of KD include fever lasting for more than 5 days, as well as at least four of the following five symptoms: diffuse mucosal inflammation with strawberry tongue and fissure lips (1 mouth), bilateral non-purulent conjunctivitis (2 eyes), unilateral cervical lymphadenopathy (3 fingers check lymph node), indurative angioedema over the hands and feet (4 limbs), dysmorphic skin rashes (5 or more skin rashes) [5]. These five KD characteristic symptoms may not be easy to remember for parents or first-line clinicians. Finding an easier technique for remembering the five characteristics of KD is important for both parents and clinicians so that KD can be identified earlier. In order to help with that, I created the "Kuo Mnemonic" to quickly recall KD diagnosis criteria [Table 1], which has been modified from our previous review [25]. According to the Japanese Circulation Society Joint Working Groups' criteria (JCS 2008, Guidelines for diagnosis and management of cardiovascular sequelae in KD) [30], KD can be diagnosed even when a fever occurs for less than 5 days. However, according to the American Heart Association (AHA) criteria (3), a fever lasting for 5 days or more is essential for a diagnosis of KD.

Bacillus Calmette-Guérin (BCG) site induration

In countries with a routine BCG immunization policy (such as Taiwan and Japan), an erythematous change over BCG scars will be observed in one-third to one-half of KD patients [4]. Tseng et al. reported that this bull's eye dermatoscopic sign is not only a useful diagnostic marker but can also serve as a severity biomarker of CAL formation in KD patients [31]. Furthermore, Uehara et al. [32] reported that redness or the formation of a crust at the BCG inoculation site is a useful sign for diagnosing KD in children. In Taiwan, the BCG vaccine schedule was changed in year 2016 to 5 month-old of age, this diagnostic sign of BCG induration cannot be used for children younger than 5 months old suspecting of having KD.

If a patient has 4 or fewer signs of the KD clinical criteria, physicians should consider redness or crust formation at the BCG inoculation site as a possible indicator of KD. Altogether, a BCG site induration change can serve as independent diagnostic criteria to help diagnose KD. If patients are suspected of having KD but do not fully fit the diagnosis criteria, the physician should further consider BCG vaccination site indurations, as well as the six items of AHA supplemental criteria for KD, consulting a KD expert, and ordering a cardiac echography [Table 2].

Consulting a Kawasaki disease expert

A KD expert (such as a cardiologist, immunologist, infectious disease specialist, or rheumatologist) should be consulted when fever lasts for ≥7 days without a definitive diagnosis. The major diagnostic criteria of KD depend on five clinical symptoms, which causes diagnosis to be subjective. No laboratory data (objective markers) are currently available to be used specifically for diagnosing KD. Consulting an expert will improve the subjectivity of making diagnosis for KD. The website *Expertscape* provides a good way to find KD experts throughout the world and can be searched according to city, area, country, and continent (www.expertscape.com).

Table 1 Rapid memory method of "Kuo Mnemonic" for Kawasaki disease diagnostic criteria.

Number	Mnemonic method	Clinical symptoms and signs
1	"One" mouth (humans have 1 mouth)	Diffuse mucosal inflammation with strawberry tongue and fissure lips
2	"Two" eyes (humans have 2 eyes)	Bilateral non-purulent conjunctivitis
3	"Three" fingers palpation neck lymph nodes (Doctors use 3 fingers to check neck for lymph nodes)	Neck lymphadenopathy (unilateral, >1.5 cm)
4	"Four" limbs changes (humans have 4 limbs)	Indurative over hands and feet (peeling in subacute stage)
5	"Five" = multiple skin rashes (5 indicates a lot)	Dysmorphic general skin rashes

*This table was modified from previous report [25].