KAWASAKI DISEASE IN INFANTS

Hung Liang Choo

Institute of Pediatrics, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Kawasaki disease (KD) is defined as an acute, self-limiting systemic vasculitis, occurring predominantly in infants and young children. It is the most commonly acquired heart disease in children in developed countries. This is a condition that is common among children of Asian origin, particularly Japanese. Dr Tomisaku saw his first case in 1961, was published in 1967 (Council on Cardiovascular Disease in the Young, 2001) and translated into English in 1974 (Dahdah *et al,* 2009).

Dr Kawasaki recorded seven characteristics from his fifty children (Fig 1): 1) Fever higher than 38 degrees centigrade for 6 days or more; 2) Non-suppurative bilateral bulbar conjunctival injection, sparing the limbic part; 3) Erythematous rash particularly on palms/soles. The rash may also present as maculopapular type or erythema multiforme, but never form vesicles; 4) Redness, dryness, erosion and cracking of the lips; 5) Acute swelling of cervical lymph nodes which was classically described to be equal to or bigger than the head of the thumbs, but never suppurate; 6) Hands and feet exhibit vasoneurogenic edema; 7) Desquamation, of which starts from the nail-skin junction of the fingers and toes mostly begin in the 2nd week of the disease.

Pathophysiology of Kawasaki disease

For over forty years of pursuing the cause, the etiology of KD remains unknown. It is now accepted that KD is the result of a hyperimmune response, triggered by an infectious agent, most likely viral, occurring in genetically susceptible

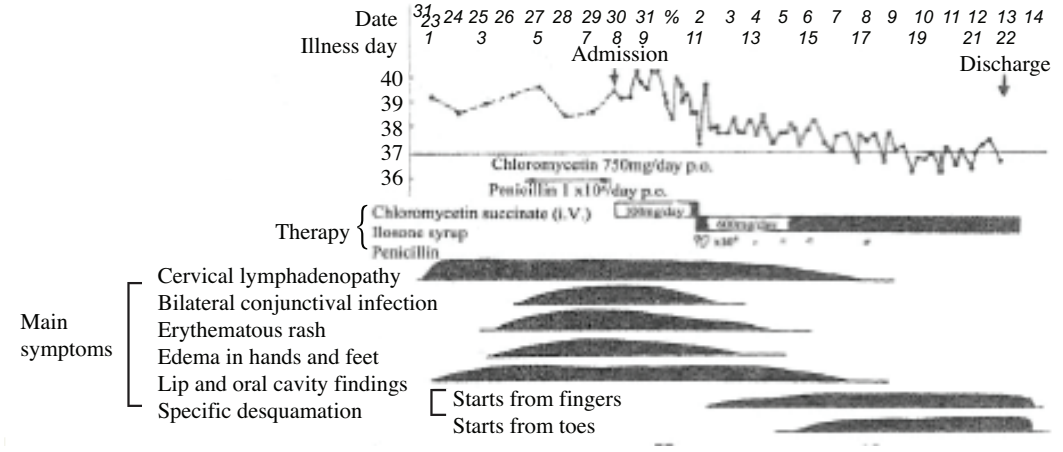

Fig 1–Clinical characteristics of Kawasaki disease.

minority. To date the specific genes has not been identified.

Diagnostic criteria of Kawasaki disease (Forsey and Mertens, 2012)

According to the American Heart Association 2001, the suggested criteria must include all three of the following: 1) Fever equal or greater than five days; 2) Four or more of the following signs/symptoms: bilateral non-exudative bulbar conjunctival injection, erythema of lips and oral mucosa, peripheral changes of the extremities, polymorphous rash, and non-suppurative cervical lymphadenopathy larger than 1.5 cm; 3) Fever without other more reasonable explanation, meaning that KD is in practice a diagnosis of exclusion.

The presence of fever for fewer days is not compulsory. Indeed, this is the practice in some circumstances where intravenous immunoglobulin is administered on Day 4 of the illness. The basis behind the guideline helps to ensure that there is no 'over-diagnosis' of KD and unnecessary referral is minimized. It is important to remember that these features of KD do not occur simultaneously. Conjunctivitis and skin rash may be transient of one or two day duration. In such cases, it is not possible to diagnose classic KD. The diagnostic dilemma of KD comprises unknown etiology and pathophysiology, compounded by the absence of pathognomonic clinical features and a specific diagnostic test.

Until 2004, a number of authorities accepted the definition of atypical KD as being the same as incomplete KD, where coronary complications were present but without the full classical diagnostic criteria. The prevalence was between 15 to 36 percent, being common in the infants and the 5-9 years age group. It was found also that these children were at a higher risk of developing coronary abnormalities due to diagnostic bias, delayed diagnosis, and late intravenous immunoglobulin (IVIG) treatment beyond day seven of the illness (Kawasaki, 1967).

In 2004, the American Heart Association suggested the terminology of KD under three headings: Classical, Incomplete, and Atypical (Kawasaki *et al,* 1974). The classical KD fulfills all the clinical features in accordance with the American Heart Association or Japanese Ministry of Health criteria. Incomplete KD is assigned to those with insufficient features. Atypical KD is used for children presenting with conditions not generally found in KD, such as renal impairment or thrombocytopenia.

The American Heart Association has an algorithm to aid with the evaluation of suspected incomplete KD; however, it is not evidence based nor has it been validated to date (Fig 2). In combination with this guideline, the practice of the speaker in Malaysia if infants present with five or more days of fever and two to three other features, then laboratory tests should be conducted. Inflammatory markers, full blood count, liver function test, and urine for white blood cell count are checked on Day 7. Incomplete KD may be diagnosed if the result is positive in three out of six supplementary tests, namely anemia for age, leukocytosis (total white blood cell count >15,000 cell/mm^3), thrombocytosis (platelet >450,000/mm^3 after Day 7 of disease), hypoalbuminemia (albumin < 3.0 g/dl), raised alanine transferase, and urine white blood cells of more than 10 per high power field. IVIG can then be given without the need for echocardiogram. For those

Fig 2–Algorithm for evaluation of suspected incomplete Kawasaki disease.

with less than three positive test results, then echocardiogram should be considered where specific evidence of coronary dilatation is sought: LAD or RCA Z-score ≥2.5, evidence of aneurysm, or ≥3 suggestive features (perivascular brightness, lack of tapering, decreased left ventricular function, mitral regurgitation, pericardial effusion).

For the suspected cases whose inflammatory markers are not raised, then daily review is recommended. If the fever subsides with no skin peeling, then no follow-up is required. Should desquamation occur, then an echo is advisable. In children who do not fit the above pathways but have persistent fever, then echo should be performed, with KD expert consultation if the results are dubious or normal.

Other useful findings include inflammation at BCG inoculation site, anterior uveitis, elevated levels of brain natriuretic peptide (Newburger *et al,* 2004; Lai *et al,* 2013), hyponatremia, elevation of LV mass and LV diastolic dysfunction, and perianal erythema or desquamation. In 2007, a Japanese nationwide epidemiologic survey on over fifteen thousand KD patients found redness or crust formation at BCG vaccination site in nearly half of them (Takeuchi *et al,* 2007). Moreover, 70% of these children were less than two years of age. The latter finding is similar to that of a Taiwanese study (Uehara *et al,* 2010). A web-based Malaysian KD Registry, recording from June 2010 to December 2012, has 305 patients where BCG scar inflammation was seen in 53% of infants.

In conclusion, one must have a high index of suspicion of incomplete KD in infants with unexplained fever for five or more days. A detailed history and repeated careful physical examinations for diagnostic features are crucial. Infants with fever for five days or more should be suspected to have incomplete KD and reassessed according to the AHA recommendations.

Re-activation or inflammation of BCG inoculation site is an important clinical feature that supports the diagnosis of KD especially in infants. Early diagnosis and treatment of infants with KD is crucial to reduce cardiac sequelae.

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