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Diagnosis and classification of Kawasaki disease

Judith Sánchez-Manubens, Rosa Bou, Jordi Anton*

Pediatric Rheumatology Unit, Hospital Sant Joan de Déu, Universitat de Barcelona, Spain

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ABSTRACT

Kawasaki disease is an acute systemic vasculitis of unknown etiology. Diagnosis is based on clinical criteria that include fever, exanthema, conjunctivitis, changes in the extremities, erythema of oral mucosa and lips and cervical lymphadenopathy. However, these criteria have low sensitivity and specificity and therefore, other clinical and laboratory features may be helpful in establishing the diagnosis, especially for cases of atypical or incomplete Kawasaki disease. Prognosis depends on the extent of cardiac involvement; coronary aneurysms develop in 20–25% of untreated patients and these may lead to myocardial infarction and sudden death. Treatment with high-dose intravenous immunoglobulin is effective in reducing the risk of coronary aneurysms in most cases and is the treatment of choice for initial Kawasaki disease.

Kawasaki disease (KD) is a systemic vasculitis that affects small and medium-sized vessels [1]. It is a self-limited inflammatory process, but potentially life threatening depending on the extent of cardiac involvement. The disease was first described by Tomisaku Kawasaki in 1967, in 50 children that presented with a mucocutaneous lymph node syndrome, high fever and a characteristic desquamation of fingers and toes [2].

1. Epidemiology

Although KD is more prevalent in Asian countries, especially in Japan, with an annual incidence that has raised to 239.6 per 100,000 children under 5 years old in 2010 [3], it has a universal distribution and can be manifested in children of any ethnicity. In the US [4], KD has a global hospitalization rate of 17.1 per 100,000 children, with higher incidence among Americans of Asian and Pacific Island descent (32.5/100,000 children <5 years old). In Europe some studies establish KD incidences between 4.9 per 100,000 children under 5 years old in Denmark [5] to 9 per 100,000 children in France [6].

KD is a pediatric disease and boys outnumber girls by 1.5–1.7:1. In most of the series, 80% of cases occur in children between 6 months and 4 years [7,8]. Some reports describe KD cases in older children, who may have a higher prevalence of cardiovascular complications related to late diagnosis [9], neonates [10,11], adults [12] and patients with HIV infection [13].

In Japan, KD has a marked bimodal seasonality with peaks in January and June/July and a nadir in October [14]. In the United States KD is also more common during winter and early spring months [4,14].

In Japan, the recurrence rate of Kawasaki disease has been reported to be 3% and the proportion of cases with a positive family history is 1% [15]. The risk of occurrence in twins is 13% [16,17].

2. Etiology and pathogenesis

The etiology of KD is still unknown, although clinical, laboratory and epidemiological features suggest an infectious origin or trigger. However, many studies have failed to identify a unique etiological infectious agent. It has also not been proved to be related to exposure to any drug or as a response to a superantigen. On the contrary, activation of immune system is an evident characteristic of KD, and concentrations of many proinflammatory cytokines and chemokines are being studied in patients with KD, which may lead to improved anti-inflammatory therapy in the future [18].

By examining tissue samples from fatal cases of KD some progress has been made in understanding KD etiology and pathogenesis. One of the currently most accepted theories [19] suggests that the disease may be caused by an infectious agent, probably a virus, which is inhaled and infects medium-sized ciliated bronchial epithelial cells. This non-identified agent is engulfed by tissue macrophages and an innate immune response is initiated. Antigens are then carried to local lymph nodes and they initiate the adaptative immune response. Bronchial epithelial cells are infiltrated by

* Corresponding author. Pediatric Rheumatology Unit, Hospital Sant Joan de Déu, Passeig Sant Joan de Déu 2, 08950 Esplugues, Barcelona, Spain. Tel.: +34 932804000, +34 665500215; fax: +34 936009460.
E-mail addresses: jsanchezm@hsjdbcn.org (J. Sánchez-Manubens), rbou@hsjdbcn.org (R. Bou), janton@hsjdbcn.org (J. Anton).

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macrophages, antigen-specific T lymphocytes and IgA plasma cells while monocytes and macrophages containing the KD agent enter the bloodstream so the agent is able to infect specific susceptible tissues (vascular and ductal tissues). In the coronary tissue, the infection leads to the secretion of vascular endothelial growth factor, matrix metalloproteinase 9, tumor necrosis factor-α and other proinflammatory cytokines. This immune reaction destroys the intima, internal and external elastic laminae of the coronary artery are fragmented and ballooning occurs leading to an artery aneurism. In the bronchial epithelium, the KD agent retreats into cytoplasmatic inclusion bodies that persist as they are not recognized by the immune system.

Other studies [20] show that molecular analysis of the oligoclonal IgA response in acute KD led to production of synthetic KD antibodies. These antibodies identify intracytoplasmic inclusion bodies in acute KD tissues. Light and electron microscopic studies indicate that the inclusion bodies are consistent with aggregates of viral proteins and RNA which have not been yet identified.

In another recent study [21], analyses of the three major KD epidemics in Japan, major non-epidemic interannual fluctuations of KD cases in Japan and San Diego, and the seasonal variation of KD in Japan, Hawaii, and San Diego, reveals a consistent pattern wherein KD cases are often linked to large-scale wind currents originating in central Asia and traversing the north Pacific. These results suggest that the environmental trigger for KD could be wind-borne.

As mentioned previously, the high incidence in Asian communities and the increased risk in siblings of cases suggest that host genetic factors are important in the pathogenesis of KD. Some genome-wide association studies (GWAS) in KD have been published [22–26] and a number of biologically plausible loci involved in inflammation, immune responses and cardiovascular status have been identified. In the largest study to date, involving 2173 individuals with KD and 9383 controls from five independent sample collections, two variants exceeded genome-wide significance. The most significantly associated variants were a non-synonymous polymorphism in a high affinity receptor for immunoglobulin G (FCGR2A) and variants in the region of the T-cell regulator ITPKC, originally reported in the Japanese [22].

A reasonable open hypothesis is that KD is caused by an infectious agent that produces disease only in genetically predisposed individuals, particularly Asians. Its rarity in the first few months of life and in adults suggests an agent to which the latter are immune and from which very young infants are protected by passive maternal antibodies.

3. Clinical manifestations

1. Fever (100%): The fever in KD is typically high spiking and remittent (in many cases >40 °C). It is often resistant to antipyretics.
2. Changes in Extremities (93%): Erythema and edema of hands and feet, which is sometimes painful, is a frequent manifestation of KD at the onset of the disease, and lasts for 1–3 days. Desquamation of fingers and toes appears in the convalescence phase (2–3 weeks after onset of fever). A subtle perineal desquamation may also be observed at the early stages of the disease. Approximately 1 or 2 months after the onset of fever, small transverse grooves across fingernails may appear (Beau's lines).
3. Exanthema (95%): The exanthema in KD is polymorphous and nonspecific. It is often an erythematous, maculopapular rash, but occasionally can appear as a scarlatiniform and micropustular rash, in some cases erythroderma can also be present. It has not been described as bullous or vesicular eruption. It can be seen during the acute phase of illness, often during the first 5 days of fever. The exanthema is usually extensive; affecting predominantly the trunk, but it can also be limited to the perineal region [27].
4. Conjunctival Injection (90%): The conjunctivitis is bilateral, painless, and nonpurulent, affecting the bulbar conjunctiva (sparing the limbus). It usually begins shortly after the onset of fever and is transient (sometimes can only be seen on the first day during the acute phase of the illness). A mild acute iridocyclitis or anterior uveitis may also be noted by a slit lamp [28].
5. Changes in Lips and Oral Cavity (93%): The lips are dry and cracked, with hemorrhagic erythema; there is a characteristic strawberry tongue with prominent papilla, and a diffuse erythema of oropharyngeal mucosal surfaces. Ulcers and pharyngeal exudates are not suggestive of KD.
6. Lymphadenopathy (43%): It is usually unilateral and confined to the anterior cervical triangle. There has to be at least one adenopathy >1.5 cm in diameter (to fulfill diagnostic criteria), although multiple adjacent enlarged nodes may be detected using cervical ultrasound.
7. Cardiologic Findings: During the acute phase of illness, an echocardiographic evaluation may reveal signs of myocarditis with decreased ejection fraction, pericarditis, mitral regurgitation and perivascular brightness of the coronary wall. Coronary aneurysms generally appear during the convalescence phase (since second week). Ideally, echocardiography should be performed at least while diagnosis, at weeks 2 and between 6 and week 8 of illness [27]. Cardiac manifestations such as myocarditis and pericarditis occur during the acute phase of illness, whereas coronary aneurysms are formed in later stages.
8. Other Clinical Findings: Clinical findings other than the classical diagnostic criteria are common in KD and may help us in diagnosis. Gastrointestinal manifestations including vomiting, diarrhea, and abdominal pain are present in approximately one-third of the patients. Gallbladder distention (hydrops) can also occur in KD [29]; in some patients, liver enlargement, transaminase elevation and jaundice have also been reported. Characteristically, patients with KD have marked irritability. This may reflect aseptic meningitis that is found in those KD patients who have had a lumbar puncture. Sensorineural hearing loss, transient or permanent [30,31], and facial paralysis are rarely present [32]. Arthritis and arthralgia may also be observed during the acute phase or convalescence, which affects both small and large joints. Induration and erythema at the site of a previous vaccination with Bacille Calmatte-Guerin has also been described [33].

4. Diagnostic criteria

The diagnosis of KD is based on the presence of at least 5 days of fever, and 4 of the five principal clinical features (Table 1) [27].

Patients with at least 5 days of fever but less than 4 principal criteria can be diagnosed with KD when coronary artery

Table 1
Diagnostic criteria for Kawasaki disease.

Fever of 5 days and presence of 4 principal features:
1 Changes in extremities: acute phase: erythema of palms and soles, and edema of hands and feet subacute phase: desquamation of fingers and toes.
2 Polymorphous exanthema
3 Bilateral bulbar conjunctival injection.
4 Changes in lips and oral mucosa: erythematous and cracked lips, strawberry tongue, and oral and pharyngeal hyperemia.
5 Cervical lymphadenopathy (>1.5 cm diameter)