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**Abstract**

Kawasaki disease (KD) is a systemic vasculitis mainly affecting children below 5 years of age. Diagnosis is made upon a combination of criteria, including persistent fever; edema, erythema, or desquamation of the extremities; polymorphous exanthema; conjunctival injection; erythema of the lips and oral mucosa; and lymphadenopathies. Many cases do not meet all diagnostic criteria but should also be considered for therapy. IVIG and aspirin are the main therapeutic measures.

**Keywords**

Vasculitis • Coronary aneurism • Perineal rash • Superantigens

**Introduction**

Kawasaki disease (KD) is a systemic vasculitis primarily affecting children. It was first described by Tomisaku Kawasaki in 1967 [1], and until today its etiology remains unknown. Diagnosis of the disease is made on clinical grounds, and KD can lead to systemic complications, including heart disease in up to 25 % of the patients [2]. KD is now considered the most common cause of acquired heart disease in children in developed countries worldwide [3].

**Epidemiology**

- **Most cases occur below the age of 5**
- **Higher prevalence in Asians**
- **Seasonal clustering in winter**

Most cases of KD occur in children under 5 years, although there have been some adult case reports [4]. Male:female ratio is 1.5:1. There is a clear seasonal relation, with exceedingly more cases diagnosed in winter and early spring [3].

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KD has a high prevalence among the Japanese population, with an incidence of 210 cases/100,000 children. Likewise, a high prevalence in Asian descendants and Pacific islander children, especially Japanese descendants living in Hawaii, has been confirmed in epidemiologic studies [5]. There are no data about its incidence or disease burden, morbidity, or mortality among Latin American children. Under reporting of cases is likely in these countries; for that reason, a research network on KD in children from Latin America was recently created [6].

Incidence among the Caucasian population in northern European countries and White non-Hispanic children in the US varies between 5.4–11.7 and 13.7 respectively [5, 7].

**Pathogenesis**

Although the etiology is unknown, it is widely postulated that KD occurs after an exposure of a genetically susceptible individual to a yet unidentified agent, possibly of infectious nature. A prospective case-control study conducted in Taiwan aiming to investigate possible links between common viral infections and KD found that cases of KD were more likely to have overall positive rates of viral PCR in throat and nasopharyngeal swabs for adenoviruses, enteroviruses, rhinoviruses, and coronaviruses [8]. KD is characterized

by an endothelial cell injury, which could be due to abnormal cytokine production and to generation of cytotoxic antibodies against the endothelial cells [9]. All data suggest that this activation of the immune system occurs after infection only in genetically predisposed individuals. The most consistently associated genetic variants are nonsynonymous polymorphisms in a high affinity receptor for immunoglobulin G (FCGR2A) and variants in the region of the T-cell regulator ITPKC, a kinase of IP3 (inositol 1,4,5-triphosphate), a second messenger molecule involved in the Ca<sup>2+</sup>/NFAT (nuclear factor of activated T-cells) pathway, or in caspase-3 (CASP-3), as confirmed in some genome-wide association studies (GWAS) [10].

## Clinical Manifestations

- **Persistent fever is the main diagnostic criterion**
- **Cutaneous and mucous manifestations are key for the diagnosis**
- **Many cases of KD do not meet diagnostic criteria**

The diagnosis of KD is made on clinical grounds according to clinical criteria; four out of the five clinical criteria involve the skin or mucous membranes.

The main criterion is fever, which must be present for at least 5 days. Fever must be present and is usually high (>39–40 °C) and resistant to antipyretics. The five clinical criteria include edema, erythema or desquamation of the extremities; polymorphous exanthema; conjunctival injection; erythema of the lips and oral mucosa; and lymphadenopathies (see Table 46.1) [11].

**Table 46.1** Kawasaki disease (KD) diagnostic criteria according to the American Heart Association [11]

Epidemiological case definition (classic clinical criteria)<sup>a</sup>

Fever persisting at least 5 days<sup>b</sup>

Presence of at least 4 principal features:

1. Changes in extremities
  - (a) Acute: Erythema of palms, soles; edema of hands, feet
  - (b) Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
2. Polymorphous exanthem
3. Bilateral bulbar conjunctival injection without exudate
4. Changes in lips and oral cavity: Erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae

5. Cervical lymphadenopathy (>1.5-cm diameter), usually

Exclusion of other diseases with similar findings

<sup>a</sup>Patients with fever at least 5 days and 4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities detected by 2-D echocardiography or angiography

<sup>b</sup>In presence of 4 principal criteria, KD diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many Kawasaki disease patients may establish diagnosis before day 4

Cutaneous manifestations are striking and should alert the clinician to the possibility of disease; they are present in 90 % of the patients [2]. A maculopapular, nonspecific exanthema may be seen accompanying the fever during the acute phase (Fig. 46.1). It can affect the trunk and sometimes involves more than 90 % of the skin (erythroderma). In other cases, it can be very subtle and affect only the perineal area or the skin folds. The changes in extremities include the erythema and edema, which can be sometimes painful. Desquamation of the tips of the fingers usually occurs later in the disease [12]. Mucous membrane manifestations include nonpurulent, bilateral conjunctivitis and hemorrhagic enanthem, with strawberry tongue with prominent papillae. A bright erythema of the lips with cracks is highly characteristic (Fig. 46.2).

At least one lymph node should be enlarged to more than 1.5 cm in diameter. Enlarged lymph nodes can be conspicuous in some cases. Heart involvement is a major risk and includes in the acute phase the presence of myocarditis or



**Fig. 46.1** Morbilliform exanthema in Kawasaki disease (KD) (courtesy Dr. Carola Durán)



**Fig. 46.2** Lip edema and cracking in KD (courtesy Dr. Carola Durán)

**Table 46.2** Other clinical and laboratory findings [11]

<i>Cardiovascular findings</i>
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size non-coronary arteries
Raynaud's phenomenon
Peripheral gangrene
<i>Musculoskeletal system</i>
Arthritis, arthralgia
<i>Gastrointestinal tract</i>
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
<i>Central nervous system</i>
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
<i>Genitourinary system</i>
Urethritis/meatitis
<i>Other findings</i>
Erythema, induration at Bacille Calmette–Guérin (BCG) inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
<i>Laboratory findings in acute KD</i>
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate (ESR)
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

pericarditis and in later stages the formation of coronary aneurysms. Other clinical findings of KD can be seen in Table 46.2.

The diagnostic criteria of KD have low sensitivity and specificity. Therefore, patients with suspected KD but who do not meet the criteria and whose diagnosis is made upon heart involvement on echocardiography are included under the umbrella term ‘incomplete KD’ [12].

## Complications and Prognosis

KD is a multisystem vasculitis, mainly involving small arteries. Coronary arteries are often affected. It is known that in the acute phase (9–10 days after fever onset) about 30–50 % of children may have a transient coronary dilatation. If left

untreated, about 15–25 % of the children will develop coronary artery aneurysms (CAAs), which can lead to myocardial infarction, sudden death, and ischemic heart disease. Myocarditis and pericarditis can also be present in the acute phase, whereas CAAs appear in the convalescence phase. The occurrence of coronary artery lesion (CAL) is associated with many factors in children with KD. Age of less than 1 year or greater than 8 years, male sex, incomplete KD, delayed IVIG treatment after onset, no response to intravenous immunoglobulin treatment, and prolonged fever duration have all been identified as risk factors for the development of CAL [13].

Mortality rates are low (0.01–0.2 %) and peak at 15–45 days after disease onset [14]. There have been some cutaneous and systemic complications in isolated case reports in the literature, including psoriasiform rash after the acute phase, pincer nails, and even Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome following aspirin administration for KD [15, 16]. Up to 2 % of cases may experience recurrence of KD [14].

## Treatment

- **Treatment is aimed to prevent heart complications**
- **IV immunoglobulin and aspirin are the first-line treatment of KD**
- **Corticosteroids do not seem to play an important role for treatment**

Treatment of KD is aimed at preventing cardiac complications. Timely IVIG treatment can be delayed by incomplete clinical signs in at least 15–20 % of children with KD. Children with incomplete KD have at least the same risk for CAA than children with KD who meet the diagnostic criteria [17].

Treatment is carried out according to the guidelines of the American Heart Association published in 2004 [11]. The current recommended therapy for KD is the combination of intravenous immunoglobulin (IVIG) 2 g/kg and aspirin 30–50 mg/kg during the acute febrile phase; once inflammation is reduced, a low antiplatelet dose of 3–5 mg/kg is used (see Table 46.3) [18].

The role of corticosteroid therapy in KD remains controversial; a meta-analysis found data indicating that corticosteroid therapy does not increase the incidence of CALs in high-risk children or patients refractory to IVIG therapy. Although the use of steroids did not significantly reduce the risk of CALs in children with KD, the data in the meta-analysis suggested that it does shorten the duration of fever and reduces the number of patients requiring retreatment with IVIG or other pharmacologic protocols [19]. Other therapies with immunosuppressive agents or anti-TNF $\alpha$  have been reported in isolated case reports or small series but cannot be recommended systematically [18].

**Table 46.3** Treatment recommendation for KD [18]

Treatment	Dosage	Recommendations
IVIG	2 g/kg	Single infusion over 10 h
Aspirin	30–50 mg/kg	Maintain dose until fever goes down, then 3–5 mg/kg
Corticosteroids <sup>a</sup>	2 mg/kg IV prednisolone	For 5–7 days, then oral prednisone taper the dose over 2–3 weeks

<sup>a</sup>Only selected patients: IVIG resistant, severe/high risk patients or patients who already had coronary and/or peripheral aneurism with ongoing inflammation at presentation

## Conclusion

Early recognition and treatment of KD are key to prevent heart complications of the disease. Attention should be paid to certain typical skin and mucous membrane manifestations, including the lip erythema and the perianal rash. Atypical cases of KD, in whom diagnostic criteria are not fully met, should be considered for treatment.

## References

- Kawasaki T, Naoe S. History of Kawasaki disease. *Clin Exp Nephrol.* 2014;18:301–4.
- Jamieson N, Singh-Grewal D. Kawasaki disease: a clinician's update. *Int J Pediatr.* 2013;2013:645391.
- Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, et al. Seasonality of Kawasaki disease: a global perspective. *PLoS One.* 2013;8:e74529.
- Sève P, Stankovic K, Smail A, Durand DV, Marchand G, Broussolle C. Adult Kawasaki disease: report of two cases and literature review. *Semin Arthritis Rheum.* 2005;34:785–92.
- Holman RC, Christensen KY, Belay ED, Steiner CA, Effl PV, Miyamura J, et al. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J.* 2010;69:194–7.
- González-Mata A, Ulloa-Gutierrez R, Brea del Castillo J, Soza G, Tremoulet AH. [Origin and importance of the Latin American Kawasaki Disease Network (REKAMLATINA)]. *Rev Chilena Infectol.* 2013;30:402–4.
- Salo E, Griffiths EP, Farstad T, Schiller B, Nakamura Y, Yashiro M, et al. Incidence of Kawasaki disease in northern European countries. *Pediatr Int.* 2012;54:770–2.
- Chang L-Y, Lu C-Y, Shao P-L, Lee P-I, Lin M-T, Fan T-Y, et al. Viral infections associated with Kawasaki disease. *J Formos Med Assoc.* 2014;113:148–54.
- Galeotti C, Bayry J, Kone-Paut I, Kaveri SV. Kawasaki disease: aetiopathogenesis and therapeutic utility of intravenous immunoglobulin. *Autoimmun Rev.* 2010;9:441–8.
- Onouchi Y. Genetics of Kawasaki disease: what we know and don't know. *Circ J.* 2012;76:1581–6.
- Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation.* 2004;110:2747–71.
- Sánchez-Manubens J, Bou R, Anton J. Diagnosis and classification of Kawasaki disease. *J Autoimmun.* 2014;49:113–7.
- Li Y, Wang X-M, Liu Y-L, Shi K, Yang Y-F, Guo Y-H. Risk factors for coronary artery lesions in children with Kawasaki disease. *Zhongguo Dang Dai Er Ke Za Zhi.* 2012;14:938–41.
- Bayers S, Shulman ST, Paller AS. Kawasaki disease: part II. Complications and treatment. *J Am Acad Dermatol.* 2013;69:513.e1–8. Quiz 521–2.
- Vanderhooft SL, Vanderhooft JE. Pincer nail deformity after Kawasaki's disease. *J Am Acad Dermatol.* 1999;41:341–2.
- Mizuno Y, Suga Y, Muramatsu S, Hasegawa T, Ogawa H. Psoriasiform and palmoplantar pustular lesions induced after Kawasaki disease. *Int J Dermatol.* 2006;45:1080–2.
- Yellen ES, Gauvreau K, Takahashi M, Burns JC, Shulman S, Baker AL, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. *Pediatrics.* 2010;125:e234–41.
- Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. *Arch Dis Child.* 2014;99:74–83.
- Zhu B-H, Lv H-T, Sun L, Zhang J-M, Cao L, Jia H-L, et al. A meta-analysis on the effect of corticosteroid therapy in Kawasaki disease. *Eur J Pediatr.* 2012;171:571–8.