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Mini Review

Kawasaki Disease: Updated Criteria and Therapeutic Strategies

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Abstract

Kawasaki disease (KD) is a common pediatric vasculitis, usually presenting with fever, bilateral non-exudative conjunctivitis, unilateral cervical lymphadenopathy, maculopapular rash, erythema of the hands and/or feet, and mucocutaneous changes of the lips and oral cavity. Although etiopathogenesis remains incompletely understood, current evidence suggests a genetic predisposition. The standard treatment includes intravenous immunoglobulin and high-dose aspirin, while severe or refractory cases may require additional immunotherapy.

KD remains a clinical diagnosis, with recent updates allowing diagnosis after four days of fever if four main features are present or even three days in select cases. High-risk groups, such as infants under six months or those with significant coronary artery involvement, require more aggressive treatment. New guidelines also address the management of patients with large coronary aneurysms. Early recognition, risk assessment, and timely intensification of therapy in high-risk patients are key to improving outcomes.

Keywords: *Kawasaki Disease (KD); Coronary Artery Aneurysms (CAA); Tumor Necrosis Factor-Alpha (TNF-α)*

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis that primarily affects small- to medium-sized blood vessels. It is typically a self-limited febrile illness, with peak incidence in children under 5 years of age [1]. The clinical presentation often includes bilateral, painless, nonexudative conjunctivitis, unilateral cervical lymphadenopathy, a maculopapular skin rash, erythema with or without desquamation of the hands and/or feet, and mucosal changes such as red, cracked lips, glossitis, or diffuse erythema of the oral mucosa or oropharynx. Importantly, not all patients exhibit every symptom, and signs may not appear simultaneously [2].

The first documented case was reported by Kawasaki, who described a 4-year-old boy with characteristic symptoms and signs: a two-week fever, bilateral conjunctivitis, cervical lymphadenopathy, red palms, generalized polymorphous skin erythema, desquamation of the hands and feet, cracked and bleeding lips, glossitis, and diffuse oral mucosal erythema. As more cases were reported, clinical course of one patient ended fatally. Autopsy revealed coronary artery aneurysms (CAA)-later recognized as major determinants of prognosis, morbidity, and mortality in KD [3,4].

Although the precise etiopathogenesis of KD remains unclear, strong evidence suggests a genetic predisposition. Additionally, it is widely considered that an unidentified infectious agent plays a triggering role [5]. The prevalence of KD is notably higher in Asian countries, particularly Japan, where the incidence reaches 264 per 100,000 children annually [6]. In contrast, significantly lower rates are reported elsewhere, such as 8.39 per 100,000 children in England [7].

Standard treatment involves intravenous immunoglobulin (IVIG) in combination with high-dose acetylsalicylic acid. Some studies also support the use of corticosteroids [8]. In cases where first-line therapy fails, alternative treatments include tumor necrosis factor-alpha (TNF-α) inhibitors, cyclosporine A, and methotrexate [9,10].

We present recent findings and updated guidelines concerning both the diagnostic criteria and therapeutic approaches for KD.

Discussion

KD remains a clinical diagnosis, as no specific laboratory marker has yet been identified. In suspected cases, a comprehensive evaluation is essential. Recommended investigations include a complete blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests, serum electrolytes, and urinalysis. Cardiac evaluation should include an electrocardiogram and echocardiography.

Recent updates to the diagnostic criteria include a key modification: fever persisting for at least 4 days, as opposed to the previous threshold of ≥5 days, in addition to four or more key clinical features that may manifest at any point during the illness, not necessarily concurrently. Notably, experienced pediatric rheumatologists may establish a diagnosis after only 3 days of fever, provided that all other criteria are fulfilled. These main features are:

- Polymorphous rash
- Bilateral, non-exudative conjunctivitis
- Oral changes (e.g. cracked lips, glossitis, erythema of the oral or oropharyngeal mucosa)
- Palmar and plantar erythema (with or without swelling or desquamation)
- Cervical lymphadenopathy, typically unilateral.

The diagnostic criteria for incomplete KD remain unchanged and apply to patients with prolonged, unexplained fever, and two or three of the five main features. Notably, in infants under 6 months with unexplained fever lasting ≥7 days and supportive laboratory or echocardiographic findings, incomplete KD should be strongly considered and treated accordingly [11].

New studies have highlighted high-risk subgroups, particularly infants under 6 months of age at diagnosis and patients with a Z score ≥ 2.5 in the right coronary artery or left anterior descending artery on initial echocardiography. These patients are at increased risk for CAA and may benefit from intensified primary therapy [11-13]. Therapeutic updates suggest that intensification of initial therapy (dual therapy) may benefit not only IVIG-resistant cases but also high-risk patients. Dual therapy consists of IVIG (2 g/kg over 8 - 12 hours) and moderate to high dosage of aspirin (30 - 50 or 80 - 100 mg/kg/day orally, every 6 hours until the patient is afebrile for 48 - 72 hours). Intensification therapy includes systemic corticosteroids (prednisolone or methylprednisolone pulse), typically co-administered with famotidine to prevent gastrointestinal complications. Biologic agents targeting TNF-α, such as infliximab (10 mg/kg IV over 2 hours) or etanercept (0.8 mg/kg subcutaneously, once weekly for three doses) may also be utilized. In refractory cases, other therapeutic options include cyclosporine (a calcineurin-NFAT pathway inhibitor), anakinra (a recombinant interleukin-1β receptor antagonist), cyclophosphamide (an alkylating agent inhibiting DNA replication) or a second dose of IVIG [11-13].

Patients with large or giant CAA are at elevated risk for thrombosis and should receive both antiplatelet and anticoagulant therapy. Recent recommendations by Jone., *et al*. suggest that even patients whose CAA regress to medium-sized should be considered for continued anticoagulation, as luminal narrowing may result from organized thrombus rather than true vascular healing. However, the optimal anticoagulant remains under debate. The use of direct oral anticoagulants as first-line agents, compared with warfarin or low molecular weight heparin, is still being evaluated [11,14,15].

Conclusion

Despite substantial advances, much remains to be elucidated in KD. Recent progress has significantly improved the diagnostic approach and overall prognosis. Updated guidelines now permit a diagnosis of KD in patients presenting with four or more key clinical features after four days of fever, a shift from previous criteria requiring five days. The diagnostic criteria for incomplete KD remain unchanged [11].

This review emphasizes the identification of high-risk pediatric patients and underscores the importance of early intensification of primary therapy to mitigate the risk of coronary complications. Additionally, patients with large CAA require both antiplatelet and anticoagulation therapy. While the optimal anticoagulant regimen remains uncertain, this area represents a critical focus for future research to guide standardized, evidence-based management strategies [14,15].

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