Review Article

Kawasaki Disease: Unveiling the Complexities of an Enigmatic Pediatric Vasculitis

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Abstract

Kawasaki disease is a critical vasculitis of childhood that principally affects the coronary arteries. The main cause of Kawasaki disease leftovers unidentified, even if an infectious agent is sturdily suspected based on clinical and epidemiologic features. A genetic predilection is also likely, based on fluctuating incidences among ethnic groups, with advanced rates in Asians. Symptoms contain fever, conjunctival injection, erythema of the lips and oral mucosa, rash, and cervical lymphadenopathy. Some children with Kawasaki disease progress coronary artery aneurysms or ectasia, ischemic heart disease, and unexpected death. Kawasaki disease is the foremost cause of acquired heart disease among children in technologically advanced countries. This article offers a summary of the analytic and treatment guidelines published by the AHA.

Keywords: Coronary Artery Aneurysm, 'strawberry' tongue, T-cell activation, interleukin-6, necrosis, Atypical Kawasaki Disease, cervical lymphadenopathy

Introduction

Kawasaki Disease (KD), first described by Dr. Tomisaku Kawasaki in 1967, is a rare but potentially devastating pediatric condition characterized by systemic inflammation and vasculitis of medium-sized vessels. Despite over five decades of research, many aspects of KD remain enigmatic, including its etiology and specific diagnostic markers.[1]

Clinical Presentation

Table No 1: Clinical symptomatic table

SL No	Criterion	Description
1	Fever	Duration of 5 days or more PLUS 4 of 5 of the following:
2	Conjunctivitis	Bilateral, bulbar, non-suppurative
3	Lymphadenopathy	Cervical, often >1.5 cm

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4	Rash	Polymorphous, no vesicles or crusts
5	Changes in lips or oral mucosa	Red cracked lips; 'strawberry' tongue; or diffuse erythema of oropharynx
6	Changes of extremities	Initial stage: erythema and oedema of palms and soles Convalescent stage: peeling of skin from fingertips

Acute Febrile Phase

KD typically begins with a high, persistent fever that lasts for at least five days. During this febrile phase, children may also exhibit various clinical features, such as conjunctival injection, oral mucosal changes, cervical lymphadenopathy, rash, and extremity changes. These clinical criteria form the basis of diagnosing KD.

Subacute Phase

After the acute febrile phase, KD enters a subacute phase characterized by desquamation of the skin, joint pain, gastrointestinal symptoms, and potential cardiovascular complications.

Diagnostic Criteria

Diagnosing KD primarily relies on clinical criteria, including fever lasting five or more days, along with at least four of the following features: changes in the oral cavity, conjunctival injection, cervical lymphadenopathy, rash, and changes in the extremities. Despite these criteria, KD remains challenging to diagnose, often necessitating careful clinical judgment.

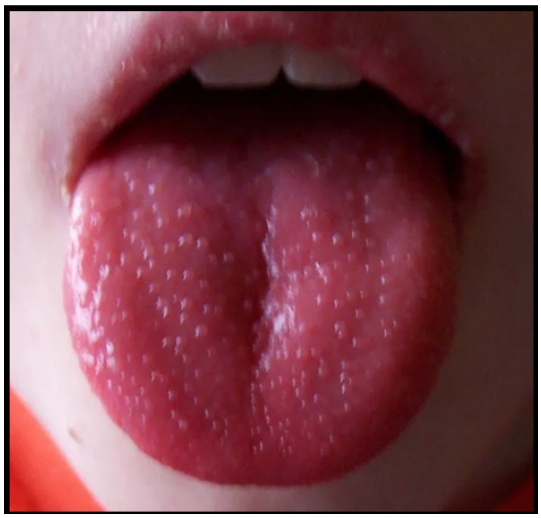

Figure 1: Strawberry tongue seen in scarlet fever and Kawasaki disease [2]

Potential Etiologies

The exact cause of KD remains elusive. Multiple factors, including infectious agents, genetics, and immune dysregulation, have been proposed as potential triggers. However, no single etiological factor has been definitively identified.

PATHOPHYSIOLOGICAL MECHANISMS

Immune Dysregulation

It is widely accepted that an aberrant immune response plays a central role in KD. There is evidence of T-cell activation, elevated cytokine levels (such as interleukin-6 and tumor necrosis factor-alpha), and dysregulated immune cell profiles.

Vascular Involvement

KD's vasculitis primarily affects medium-sized arteries, including the coronary arteries. Endothelial cell dysfunction, inflammation, and the formation of coronary artery aneurysms are key pathophysiological features.

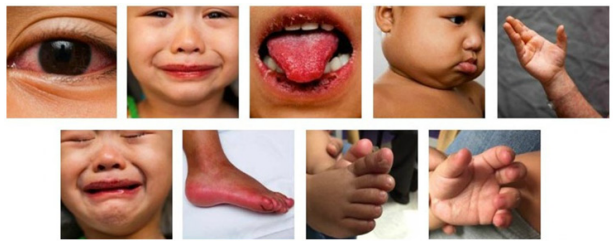

Figure 2: Various symptoms of Kawasaki disease [3]

CARDIOVASCULAR COMPLICATIONS

Coronary Artery Aneurysms (CAA)

One of the most feared complications of KD is the development of CAAs, which can lead to myocardial infarction or sudden death. Early diagnosis and prompt treatment with intravenous immunoglobulin (IVIG) can reduce the risk of CAA formation.

Myocarditis and Pericarditis

KD can cause inflammation of the myocardium and pericardium, leading to myocardial dysfunction and pericardial effusion. Echocardiography is essential for monitoring cardiac involvement.

DIAGNOSTIC CRITERIA

AHA Criteria

The diagnosis of KD relies on clinical criteria established by the AHA. According to the AHA criteria, KD is diagnosed if a patient exhibits fever for five or more days along with at least four of the following clinical features: rash, bilateral conjunctival injection, cervical lymphadenopathy, changes in the oral mucosa, and changes in the extremities.

Laboratory Findings

Laboratory tests may reveal elevated inflammatory markers, such as CRP & ESR. Additionally, a CBC may show leukocytosis, often with a left shift. However, these findings are non-specific and should be interpreted in the context of clinical presentation.[4]

REVIEWS OF THE DISEASE

Review 1: "Epidemiology and Global Problem of Kawasaki Disease"

Kawasaki Disease (KD) is an intriguing condition with a unique epidemiological pattern. It predominantly affects young children, with peak incidences in East Asian countries, particularly Japan. A retrospective study by Makino et al. (2018) provided insights into the global epidemiology of KD, emphasizing the higher incidence rates in Asian populations. The exact cause of this geographical predilection remains unclear, with theories ranging from genetic susceptibility to environmental factors. Understanding the epidemiology of KD is essential for early diagnosis and appropriate management, particularly in regions with a lower incidence rate.[5]

Review 2: "Immunopathogenesis of Kawasaki Disease"

The immunopathogenesis of Kawasaki Disease (KD) continues to be a subject of intense research. Recent work by Rowley et al. (2020) highlighted the pivotal role of the immune system, particularly innate and adaptive responses, in the development of KD. The presence of activated T cells, pro-inflammatory cytokines, and chemokines contributes to the systemic vasculitis seen in KD patients. Identifying these immunological mechanisms is crucial for developing targeted therapies that can modulate the inflammatory response and reduce the risk of coronary artery complications.[6]

Review 3: "Coronary Artery Complications in Kawasaki Disease"

One of the most significant concerns in Kawasaki Disease (KD) is the development of coronary artery complications, including aneurysms. A retrospective study by Sleeper et al. (2019) assessed the long-term outcomes of children with coronary artery aneurysms due to KD. The study underscored the importance of ongoing cardiovascular monitoring and early intervention to mitigate the risk of adverse coronary events. These findings emphasize the need for continued research into effective treatments to prevent and manage coronary artery complications in KD.[7]

Review 4: "Diagnostic Challenges and Criteria in Kawasaki Disease"

Diagnosing Kawasaki Disease (KD) can be challenging due to its variable clinical presentation and the absence of a definitive diagnostic test. A systematic review by Manlhiot et al. (2018) assessed the accuracy of various diagnostic criteria, including the AHA criteria. The study highlighted the limitations of solely relying on clinical criteria and advocated for the use of additional tools, such as biomarkers and echocardiography, to enhance diagnostic accuracy. This review underscores the ongoing efforts to refine and improve the diagnostic criteria for KD.[8]

TREATMENT MODALITIES

Intravenous Immunoglobulin (IVIG)

The primary treatment for KD is high-dose IVIG administered along with aspirin. IVIG reduces inflammation and the risk of coronary artery aneurysms. Aspirin is used to alleviate fever and prevent blood clot formation.

Corticosteroids

In cases of refractory KD or patients at high risk

for coronary artery complications, corticosteroids may be considered as an adjunct therapy. Though, their use leftovers controversial due to probable side effects.

ONGOING RESEARCH

Genetic Studies

Research into the genetic basis of KD is ongoing. Some studies suggest a genetic predisposition, and identifying specific genetic markers could enhance our understanding of the disease.

Immunomodulatory Therapies

Developing targeted immunomodulatory therapies is a focus of current research. New treatments aim to reduce inflammation while minimizing side effects.

Biomarkers for Early Diagnosis

The search for specific biomarkers that can aid in early diagnosis is ongoing. Identifying reliable markers could streamline treatment initiation.

REAL EXAMPLES

Case Study 1: "Infant Kawasaki Disease with Classic Symptoms"

Patient Profile:

A 9-month-old male infant presented with a high fever persisting for five days, accompanied by erythematous rash, bilateral non-purulent conjunctivitis, and strawberry tongue. Physical examination revealed cervical lymphadenopathy. Laboratory tests indicated elevated inflammatory markers.

Diagnosis and Treatment:

Based on clinical criteria, the patient was diagnosed with Kawasaki Disease (KD) and promptly started on IVIG therapy and high-dose aspirin. Fever subsided within 24 hours of IVIG infusion, and aspirin was continued in anti-inflammatory doses during the convalescent phase.[9]

Case Study 2: "Kawasaki Disease Complicated by Coronary Artery Aneurysm"

Patient Profile:

A 4-year-old female was diagnosed with KD based on the presence of fever, bilateral conjunctival injection, cervical lymphadenopathy, and changes in the oral mucosa. Despite timely IVIG therapy, she developed CAA.

Treatment and Follow-up:

The patient received ongoing care with frequent echocardiograms to monitor the progression of CAA. Low-dose aspirin was continued for antithrombotic prophylaxis. The long-term goal is to minimize the risk of thrombosis and stenosis in the coronary arteries.[10]

Case Study 3: "Atypical Kawasaki Disease in an Adolescent"

Patient Profile:

A 15-year-old male presented with prolonged fever, sore throat, and cervical lymphadenopathy. He exhibited fewer classic KD symptoms. Laboratory tests indicated elevated inflammatory markers and coronary artery abnormalities on echocardiography.

Diagnosis and Treatment:

Despite the atypical presentation, the patient was diagnosed with KD based on clinical criteria. IVIG therapy and aspirin were administered promptly to reduce inflammation and prevent coronary complications.[11]

Case Study 4: "Unfinished Kawasaki Disease in a Toddler"

Patient Profile:

A 2-year-old female presented with fever and irritability but did not exhibit the full spectrum of KD symptoms, such as conjunctivitis or rash. Laboratory tests showed elevated inflammatory markers.

Diagnosis and Treatment:

Although the patient did not meet all classic criteria, the clinical presentation, elevated inflammatory markers, and echocardiographic findings of coronary artery dilatation led to the

diagnosis of incomplete Kawasaki Disease. IVIG therapy and aspirin were initiated, leading to resolution of symptoms.[12]

Case Study 5: "Kawasaki Disease Reappearance in a School Going Child"

Patient Profile:

A 7-year-old male previously diagnosed with KD at age 3 presented again with fever and skin rash. Recurrent KD was suspected due to the characteristic clinical features, although the patient had a longer fever-free interval.

Diagnosis and Treatment:

Recurrent KD was confirmed based on clinical criteria, and the patient received IVIG therapy and aspirin. The recurrence highlights the importance of long-term follow-up for patients with a history of KD.[13]

Conclusion

Kawasaki Disease remains a complex and enigmatic pediatric vasculitis, necessitating further research to elucidate its etiology, improve diagnostic accuracy, and enhance treatment outcomes. Timely recognition of KD's clinical criteria and appropriate management with IVIG and aspirin are critical in preventing severe cardiovascular complications. Continued research efforts are vital for providing the best care for affected children and minimizing long-term sequelae.

List of Abbreviations:

AHA-American Heart Association

CRP-C-reactive protein

ESR-Erythrocyte sedimentation rate

IVIG-intravenous immunoglobulin

CAA-Coronary artery aneurysms

CBC-Complete blood count

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