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Review Article

Kawasaki disease – A common childhood vasculitis

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ABSTRACT

Kawasaki disease (KD) is an acute self-limiting vasculitis of children predominantly affecting the medium sized arteries. The disease was first described by Dr. Tomisaku Kawasaki in 1967 from Japan. KD has now been reported from more than 60 countries and is the commonest cause of acquired heart disease in children in the developed countries. Japan reports the highest incidence of KD at 265/100,000 children below 5 years, followed by Korea and Taiwan. In North America and Europe, the incidence of KD is much lower (9–25/100,000 children below 5) and appears to have plateaued down over the last few decades. The reasons for these differences in epidemiology are not clearly understood. KD has been increasingly reported from India over the last 20 years. At Chandigarh, an incidence of 4.54/100,000 children below 15 years was reported in 2011. However, this was likely to be an underestimate.

The etiology of KD remains unknown. Although a genetic basis of KD seems plausible, an intercurrent infectious process seems to act as a trigger for the inflammatory cascade. Like many other vasculitides, the diagnosis of KD is essentially clinical and is based on a set of criteria first elaborated by Dr. Kawasaki himself. However, several children (especially infants) with KD can have incomplete and atypical presentations. This can result in diagnostic and therapeutic delays. Approximately 15–25% children with KD can develop coronary artery abnormalities (CAAs) if left untreated. Two dimensional echocardiography remains the gold standard in detecting CAAs in patients with KD. Dual source CT coronary angiography is a recent advance in accurate detection of CAAs with minimal radiation risk. Intravenous immunoglobulin (2 g/kg) remains the drug of choice and is administered as an infusion. Other therapeutic agents that have been used include infliximab, cyclosporine, glucocorticoids, and statins. KD has been associated with several long-term sequelae.

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1. Introduction

Kawasaki disease (KD) is an acute, often self-limiting, systemic necrotizing vasculitis predominantly affecting the medium sized arteries especially the coronaries.1,2 Involvement of coronary arteries occurs in 15–25% of untreated patients and is the major cause of morbidity in this condition.1,2

The condition was first reported in 1967 by a Japanese pediatrician, Tomisaku Kawasaki. He described 50 children with a typical constellation of clinical findings that did not fit into any known medical condition. He christened the disease...
as ‘Mucocutaneous lymph node syndrome’. Soon thereafter Marian Melish from Hawaii, United States, reported cases with similar clinical findings. KD is now reported from all continents and is considered to be one of the commonest vasculitic disorders in children.

2. Epidemiology

Two distinct epidemiologic patterns of KD have been recognized. In North America and Europe the incidence of KD has stabilized and varies between 9 and 25/100,000 children below 5. There has been no perceptible increase in incidence on a decadal basis in these regions. On the other hand, countries in the Far East (like Japan, Korea and Taiwan) have been showing an increasing incidence on a decadal basis. In Japan the reported annual incidence is 265/100,000 children below 5 and this is the highest incidence reported so far from anywhere in the world. Korea reports an incidence of 134.4 while in Taiwan the figure is 82.8. Japan has reported three well-documented nationwide epidemics of KD in the years 1979, 1982 and 1986.

A hospital based study at Chandigarh had shown the incidence to be 4.54/100,000 children below 15, but this was probably an underestimate. KD appears to have some predilection for children of Asian ancestry. Studies from the United Kingdom have shown that the incidence was more than double in Asian children when compared to Caucasian and African children.

KD predominantly affects children in the pre-school age group with 80% children being below 5. KD is uncommon below 3 months of age, although it has been reported even in neonates. In Japan, the highest incidence occurs in 9–11 months old boys and 3–8 months old girls, whereas in North America, peak age is 2–3 years. In India, almost one-third of children with KD are reported to be above 5 years.

KD affects boys more commonly than girls, with male-to-female ratio varying between 1.36:1 and 1.62:1. Seasonal incidence has been noted in several countries. In Japan more cases are seen in the months of January and July. At Chandigarh, peak incidence is seen in the months of May and October with a nadir in February.

3. Etiopathogenesis

The cause of KD remains a mystery despite extensive research. Occurrence of this disease in epidemics, predilection for infants and young children and clinical features such as a febrile exanthema and cervical lymphadenopathy suggest an infectious etiology. However, there has been no confirmatory evidence in favor of a specific microbe. A host of infectious agents have been ‘linked’ with KD or incriminated in the pathogenesis of the disease. These include coronavirus, parvovirus, Staphylococcus aureus, Epstein–Barr virus, chlamydia and mycobacteria. Staphylococcal and streptococcal superantigens have been hypothesized as triggering agents in the cascade of KD. The infectious theory of KD cannot, however, explain all aspects of pathogenesis of this condition.

It has been suggested that a ‘genetic predisposition’ facilitates the development of KD in the context of an appropriate infectious insult. Exciting new work on understanding the pathogenesis of KD has unraveled the role of several signaling pathways, which have improved our understanding of this fascinating disease. The pathway associated with calcineurin-nuclear factor of activated T-cells was one of the first that was studied in this regard. This pertains to a single nucleotide polymorphism (SNP) on chromosome 19q13.2 which affects the gene for 1,4,5-trisphosphate 3-kinase C. This SNP has been linked to increased susceptibility to KD. A direct clinical correlate has been the use of calcineurin inhibitors in patients with refractory KD. The pathway associated with transforming growth factor-β (TGFβ) signaling has been linked to increased risk of coronary artery abnormalities (CAAs). A direct clinical correlate of this has been the initiation of clinical trials for use of atorvastatin in KD. The third pathway relates to a SNP in the FGFR2A that has been identified in KD patients of European descent and appears to influence susceptibility to this disease. Given the differences in genetic background between Caucasians and populations residing in the Far East, it is quite likely that the genetic basis of KD in Japan may turn out to be very different from, say, that in the United States. And that may also partly explain the differences in clinical phenotype of KD that have been reported from various parts of the world.

4. Pathology

The pathological changes are most marked in medium sized arteries, especially the coronaries. Many other arteries can also be involved – these include the subclavian, brachial, axillary, iliac or femoral vessels, and occasionally the abdominal aorta and renal arteries. The acute stage of KD lasts approximately 2–3 weeks and is characterized by edema of endothelial and smooth muscle cells with an inflammatory cell infiltrate, which is initially polymorphonuclear and later replaced by macrophages, lymphocytes (primarily CD8+ T cells) and plasma cells. The inflammatory process affects all three layers of the vascular wall, with destruction of internal as well as external elastic lamina. When the weakened arterial wall can no longer withstand its internal pressure, it becomes dilated and deformed, thereby leading on to aneurysm formation. Thrombi may develop in the vascular lumen further obstructing the blood flow. Over time, healing occurs in the vessel wall and this results in fibrosis and marked intimal proliferation which may manifest on imaging as stenotic lesions.

5. Clinical manifestations

Clinically KD can be divided into three phases – acute, subacute and convalescent phases.

Acute phase (initial 10–14 days): Fever, extreme irritability, bilateral non-exudative conjunctival injection, red (and often cracked) lips and mouth, strawberry tongue, edema
over dorsum of hands and feet, a polymorphous rash, cervical lymphadenopathy (usually unilateral) are the usual presenting features in the acute phase of KD. Myocarditis is also common in this phase. Pericarditis, hydrops of the gallbladder and perineal desquamation are other early features of KD. There may be redness and crusting at the BCG inoculation site (more common in infants).

Subacute phase (2–4 weeks): Most of the acute symptoms subside by this time. Periungual desquamation is typically seen in this phase. In some children arthritis of one or several joints can develop. CAAs are most commonly seen during this phase.

Convalescent phase: By this time, all clinical signs have generally disappeared. This phase lasts for approximately 6 weeks. By the end of this phase, the acute phase reactants (especially the CRP and the elevated platelet counts) settle down. It is towards the end of the convalescent phase that Beau’s lines over the nails may first appear.

6. Epidemiologic case definition (clinical criteria)

Fever persisting for at least 5 days
Presence of at least 4 of the following principal features:

Acute:
Erythema of palms, soles; edema of hands, feet
Subacute:
Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthema
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity:
Erythema, lip cracking, strawberry tongue
Diffuse injection of oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Exclusion of other diseases with similar findings

- Patients with fever at least 5 days and <4 principal criteria can be diagnosed with KD when CAAs are detected by two dimensional echocardiography.
- In the presence of 4 or more principal criteria, KD diagnosis can be made on day 4 of illness.

7. ‘Atypical’ and ‘incomplete’ KD

Newburger et al. described KD as ‘atypical’ or ‘incomplete’ when a patient presents with less than the required criteria for the diagnosis. Kim in a review article used ‘atypical’ and ‘incomplete’ KD interchangeably. Characteristic echocardiographic evidences of CAAs support the diagnosis of KD in such cases. The term ‘incomplete’ is preferred when there are less than 4 principal criteria and ‘atypical’ is preferred when presentation is unusual (stroke, nephritis, cardiac tamponade, hepatitis, etc.). ‘Incomplete’ KD is more common in young infants. High degree of suspicion is necessary in these group of patients for diagnosis of KD as the incidence of CAAs is higher among them. It may be noted that children with ‘incomplete’ or ‘atypical’ KD are not at lesser risk of coronary artery involvement as compared to children with typical KD.

8. Cardiovascular findings in KD

KD can lead to involvement of any part of heart starting from coronary arteries to endocardium. In early phase of the disease there may be hyperdynamic precordium, gallop, flow murmurs in presence of anemia and fever. Myocarditis is clinically manifested by unexplained tachycardia and a decreased left ventricular ejection fraction. Mild mitral regurgitation can occur. Pericarditis with pericardial effusion can be detected in the early part of the disease. CAAs are responsible for the morbidity (and also occasional mortality) associated with KD. These can develop in 15–25% of untreated patients. Giant aneurysms (>8 mm internal diameter) have a risk of rupture, development of thrombosis and later on arterial stenosis. KD is an important cause of myocardial infarction in children.

9. Other clinical findings in KD

KD is a vasculitic disorder and can affect many different organ systems. The clinical presentation of children with KD can be vastly variable. Arthritis or arthralgia is a common finding in KD. Children can present with involvement of multiple joints including interphalangeal joints and large weight bearing joints during the first week of illness. Joint involvement after 10 days of illness is usually limited to large weight bearing joints, mainly ankle and knee. Some children can present with predominant gastrointestinal complaints such as diarrhea, vomiting and pain abdomen. These can mask the clinical manifestations of KD and result in diagnostic delays. At Chandigarh, we have had several children with KD who were first admitted in the Pediatric Gastroenterology Unit before being referred. Rarely, acute surgical abdomen can be a presenting feature in KD. Hydrops of gallbladder can develop in children with KD during the acute phase of the illness. Icterus is also reported as a presenting feature of KD.

Other unusual clinical manifestations include unilateral facial nerve palsy, transient sensorineural hearing loss, pleural effusion (occasionally hemorrhagic), testicular swelling and macrophage activation syndrome.

10. Laboratory investigations

KD remains a clinical diagnosis and no laboratory investigation is pathognomonic. However, several laboratory parameters may support the clinical diagnosis.
Hematological: Leukocytosis, shift of differential leukocyte count towards left and toxic granulation of neutrophils are particularly seen during first week of illness. Rarely neutropenia can occur. The platelet count is usually normal in the first week of illness. Thrombocytopenia, which may appear during early phase of the disease, is a significant risk factor for development of coronary artery aneurysm. Presence of thrombocytopenia in KD indicates development of disseminated intravascular coagulation or macrophage activation syndrome.\(^2^5\)\(^3^5\) Thrombocytosis, which is characteristic of the disease, usually appears in the second week, and peaks in the third week. In uncomplicated cases platelet count gradually normalizes by 4–8 weeks. The mean peak platelet count is 7,00,000/mm\(^3\) but, it may be as high as (even more than) 1 million/mm\(^3\). Anemia, which is normocytic and normochromic, can be detected in 50% of patients within the first 2 weeks of illness. It is more common with prolonged active inflammation and a significant predictor of development of CAAs.\(^2^8\)\(^3^6\)

Urine examination: Sterile pyuria, usually of urethral origin can be found in 33% of patients with KD.\(^1^3\)

Biochemical abnormalities: Up to 40% of patients with KD can have mild elevations of transaminases and in 10% there can be hyperbilirubinemia.\(^2^8\) Hypoalbuminemia is more common and its presence indicates a severe form of disease. Several alterations in the serum lipid profile have been described in children with KD, and some of these may persist for several months after the acute episode.\(^2^8\)

Cerebrospinal fluid examination (CSF): CSF examination is not mandatory for the diagnosis of KD. In 50% of patients it demonstrates mononuclear cell predominance with normal glucose and protein levels (aseptic meningitis).\(^2^8\)

Imaging studies.

Echocardiography: Two dimensional echocardiography remains the gold standard for detection of CAAs in KD. During the acute stage the coronary arteries appear ‘bright’ on echocardiography. CAAs include aneurysms, ectasia and stenoses. For accurate assessment of CAAs, Z scores need to be calculated. However, echocardiography has some significant limitations. It is highly operator dependent and there is no gaining the fact that inaccuracies may creep in if the operator is not appropriately trained. Further, performing echocardiography on a sick and irritable child requires skill and patience. Echocardiography can only delineate the proximal sections of coronary arteries, and the circumflex artery may be very difficult to view.

Dual source CT coronary angiography: This is a recent advancement in the accurate detection of CAAs in patients with KD with minimal radiation risk. The important advantage over echocardiography is its ability to detect proximal as well as distal arterial abnormalities. With modern technologies available with such machines the radiation dose can be reduced to minimal levels (<1 mSv).\(^3^7\) At our center, we have started carrying out this investigation in cases wherein echocardiographic findings are equivocal. We have also used this modality for follow-up of patients with large CAAs detected on echocardiography.

11. Treatment

The main objective of the management of acute KD is to reduce the risk of development of CAAs.

Intravenous immunoglobulin (IVIg): IVIg remains the drug of choice for KD. IVIg is believed to exert anti-inflammatory and immunomodulatory effects through regulation of the inflammatory cytokine production, induction of the anti-inflammatory cytokines, suppression of bacterial superantigens or other antigens, augmentation of T-reg cell and suppressor T-cell activity, reduction of antibody production, and provision of anti-idiotypic antibody. The precise mechanism of action of IVIg in KD, however, is not clearly understood. The dose of IVIg is 2 g/kg given as single infusion. Treatment is most effective when instituted within 10 days of illness. However, it has also been noted that initiation of IVIg treatment before Day 5 of fever can sometimes result in refractory KD and this may mandate additional therapy.\(^2^8\) Vaccination against varicella and measles should be deferred till 11 months post IVIg.

Aspirin: It is believed that high dose aspirin (30–50 mg/kg/d, in 4 divided doses) along with IVIg in acute KD has additive anti-inflammatory effect.\(^2^7\) The dose can be reduced to 3–5 mg/kg/d (anti-platelet effect) once the patient is febrile for at least 48–72 h. At some centers, however, high-dose aspirin is continued for longer periods. Aspirin at anti-platelet dose to be continued for 6–8 weeks if there were no CAAs on serial echocardiography. In patients with CAAs, aspirin may be continued for indefinite period.\(^2^8\)

Treatment of IVIg resistant (refractory) KD: The term resistant KD is used, when there is persistent or recrudescent fever ≥36 h after completion of initial dose of IVIg. It can be seen in 10–15% of patients and increases the risk for CAAs. Treatment of this type of KD can be very challenging. Therapeutic options include a second dose of IVIg (2 g/kg), intravenous pulse methylprednisolone (30 mg/kg/d for 1–3 days) or infliximab.\(^3^8\)\(^3^9\) Infliximab is administered in doses of 5–10 mg/kg as a single intravenous infusion.\(^2^8\)

Other therapeutic modalities that have been tried in children with refractory KD include plasma exchange,\(^2^7\)\(^2^8\)\(^3^6\) cyclosporine A,\(^2^7\)\(^4^0\) and statins.\(^4^0\)

Prevention of thrombosis in patients with CAAs: All patients with persisting CAAs should be continued on aspirin. Children with giant coronary aneurysms also need additional anticoagulation (fractionated heparin or warfarin). Clopidogrel has been used in addition to aspirin in some cases and may be considered as an additional agent in children with large aneurysms.\(^2^8\) These agents are generally continued till CAAs show anatomic resolution.

Follow-up: Repeat echocardiography should be carried out if the fever persists even after IVIg has been administered. In such cases an increase in ‘Z’ scores of the coronary arteries may mandate additional therapy. In cases where the response to IVIg has been satisfactory, follow-up echocardiography examinations are recommended at 4–6 weeks after onset of the disease. Further evaluation of coronary arteries depends upon their status on follow-up. Angiographic resolution of coronary aneurysms observed in 50–67% of patients by 1–2 years after the illness.\(^2^8\)\(^2^9\) The likelihood of resolution is greater if size is smaller, age at onset <1 year, fusiform
aneurysm and location of aneurysm at distal coronary segment. Giant aneurysms seldom show complete resolution and often result in coronary stenosis thereby predisposing to thrombosis. Highest risk of myocardial infarction occurs during the first year after onset of illness. All children with KD should be advised heart-healthy diet, regular exercise, at least once yearly serum lipid profile and ECG/stress test as required.

12. Conclusion

KD is a common vasculitic disorder of children and is being increasingly recognized. It should be considered in the differential diagnosis of all children with fever persisting beyond 5 days. As the clinical presentation can be very variable, it is not difficult to understand how the diagnosis of KD can often be delayed or missed altogether. KD is a medical emergency. Delays in diagnosis and initiation of appropriate therapy can have catastrophic consequences. Most of the CAs regress over time but, giant aneurysms are less likely to resolve. Structural and functional abnormalities in the arterial segment may, however, persist even after regression of the aneurysm.

Conflicts of interest

The authors have none to declare.

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