A REVIEW ARTICLE: - KAWASAKI DISEASE DURING THE COVID-19 PANDEMIC

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Abstract: Kawasaki disease is distinguished by a multi system disorder with acute inflammatory processes in the small and large vessels, especially in the coronary arteries of particularly children. The primary theory for the pathogenesis is that an undisclosed infectious agent leads to the activation of the immune system in a child that is genetically susceptible to a viral or bacterial attack. There exists no direct diagnostic method for Kawasaki disease, hence a combination of clinical criteria and laboratory findings have to be run. Primary treatment measures for this disorder involve the use of a combination of intravenous immunoglobulin and aspirin.

Keywords: Kawasaki disease, Pediatrics, India, Diagnosis, Treatment

Introduction
In 1967, a Japanese pediatrician reported the first occurrence of Kawasaki disease.1 Children make up the majority age group of people affected by this and they are predominantly younger than 5 years old. Pediatric boys are more likely to have the disease occurrence with a greater risk of 1.5 more likelihood of it being present in them than compared to girls. It is however still considered to rarely occur in children below 6 months old.2 Understanding of the long-term cardiac comorbidity that may present itself in KD patients and therapy optimization in infancy to curtail the risks in adulthood and to guarantee the maintenance of evidence-based quality care for KD patients as they transition into adulthood is imperative.3 When left untreated, KD can lead to various other complications such as coronary artery aneurysms, thrombosis, and even sudden death.4 Since the Corona virus disease 2019 pandemic, it has been reported that while more than 90% of children with the virus were described to have been symptom less or had mild to moderate disease, new concerns were revealed such as new reports on hyper inflammatory malignancies or disease presenting with Kawasaki-like symptoms. Some pediatric patients had been noted as having developed cytokines storm syndrome which presented itself as fever, inflammation, and single or multi-organ dysfunction. This condition was aptly named Multi system Inflammatory Syndrome in Children (MISC-C)5

Etiopathogenesis
Kawasaki disease’s Etiopathogenesis has been studied to a great extent however much remains to be known. A theory proposed whereby there happens to be an interaction between genetic susceptibility and infectious triggers which is then followed by the development of an abnormal immune response. A genetic contribution is suspected that escalates the chances of acquiring KD and subsequently the formation of coronary artery lesions.6 Various infectious agents, bacteria alike, such as Streptococcus pyogenes and Staphylococcus aureus, and viruses like adenovirus and enteroviruses have been implicated in the pathogenesis of KD.7 The primary theory for the pathogenesis of KD is that an undisclosed infectious agent leads to activation of the immune system in a child that is genetically susceptible to a viral or bacterial attack.1 The post-infection inflammatory attack primarily targets the medium-sized muscular arteries, most commonly the coronary arteries with an initial infiltrate are primarily neutrophilic within the first two weeks. This is then followed by infiltration of eosinophils and CD8 T cells > 2 weeks after the disease presents itself.7 Some non-parenchymal vessels are involved, the coronary arteries remain the most severely affected, and chronic damage is a more foreseen feature after long-term infection. The knowledgeable theory surrounding the mechanisms underlying the onset and perpetuation of vascular inflammation is still poorly understood despite extensive research being carried out.8

Epidemiology
In India
Data retrieved from China and India, indicate that KD is now being increasingly recognized. Prior to 1990, only 3 published reports were published on KD from India. Over the last 20 years, however, several centers in India have started making notes and reporting KD. Kerala, one of the more developed states in India, also reports the largest number of cases of KD. In Chandigarh, A hospital-based study showed an increment in the incidence of KD from 0.51 per 100,000 children below 15 years from 1994 to 4.5 per 100,000 children below 15 years of age in 2007. Peak occurrence was observed to be in October with February being the lowest point. A follow-up study found the mean KD prevalence in Chandigarh from 2009 to 2014 to be 5.35 per 100,000 children below 5 years.9

Rest of the World
Vasculitis is defined as the inflammation of blood vessels and Kawasaki disease is the second most common Vasculitis illness in childhood after Henoch Schönlein purpura and the commonest cause of acquired heart disease in the pediatric population in developed countries.1 Geographical location plays a prevalent role in epidemiological patterns with variations in incidence based on ethnicity and seasons. Asians and Pacific Islanders have an incidence likelihood rate of 2.5 times the normal and in the African community, the incidence rate is 1.5 times more when compared to Caucasians. This is also backed up by the fact that Hawaii, with
the highest Asian population, has the highest incidence of KD in the USA averaging about 50.4/100,000 cases between 1996 and 2006 in children below 5 years of age which remained relatively stable. Case series of Kawasaki disease that was linked to SARS-CoV-2 were published which revealed a correlation between the virus and KD in the United Kingdom, Italy, and The United States of America. Japan documents approximately 12,000 new cases each year while in the United States, the rate of prevalence appears to have remained relatively stable. Seasonal KD presence has been noted in Taiwan whereby KD occurs most frequently in the summer months of April to June and least frequently during the winter. Seasonal occurrence varies in other countries for an unknown reason.

**Diagnosis**

No direct diagnostic test for Kawasaki disease exists, thus a combination of clinical criteria and laboratory findings have to be run concurrently to come to a definite conclusion.

Table 1. American Heart Association guidelines for the diagnosis of Kawasaki disease (2017)

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<th>Classic KD diagnosed with a fever persisting for at least 5 days</th>
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<td>At least four of the five principal clinical features:</td>
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<td>2. Changes in extremities</td>
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<td>3. Acute: Erythema of palms, soles; edema of hands, feet</td>
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<td>4. Sub acute: Periungual peeling of fingers and toes in weeks 2 and 3</td>
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<td>5. Polymorphous exanthema (diffuse maculopapular, urticarial, erythoderma, Erythema-multiforme-like, not vesicular or bullous)</td>
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<td>6. Bilateral bulbar conjunctival injection without exudates</td>
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<td>7. Cervical lymphadenopathy (&gt; 1.5 cm diameter), usually unilateral</td>
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<td>8. A careful history may reveal that ≥ 1 principal clinical features were present during the illness but resolved by the time of presentation</td>
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<td>9. Exclusion of other diseases with similar findings (e.g., scarlet fever, viral infections like measles, adenovirus, enteroviruses, Stevens-Johnson syndrome, toxic shock syndrome, drug hypersensitivity reactions, systemic juvenile idiopathic arthritis)</td>
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For children with a fever lasting for more than 5 days, KD should be considered as a diagnostic possibility. Some clinical features of KD such as conjunctival injection, cervical lymphadenopathy, and rash also present themselves as common features of illnesses like measles, rubella, adenoviral, and enteroviral viral infections with scarlet fever being seen as one of the closest mimics of this disease. Edema on the dorsum of the patient’s hands and feet as well as characteristic exfoliation which is perianal in the first few days and Periungual after days 10-12, is typical of KD.

**Treatment of Kawasaki Disease**

Acute phase treatment: The AHA (American Academy of Pediatrics) and AAP (American Associations of Pediatricians) both recommend aspirin and IVIG combination drug therapy for treating acute KD. In the late 1980s definitive clinical trials in disease treatment demonstrated the efficacy of treatment with IVIG coupled with a high-dose aspirin when administered by the tenth day of illness. This mode of therapy was compared with a standalone aspirin therapy and it was found to be more fruitful in the outcome. The recent AHA 2017 guidelines have suggested a simplified management protocol for children with KD. Therapies other than IVIG are now being increasingly used in these patients.

**Intravenous Immune globulin (IVIG)**

IVIG is seen to have a universal anti-inflammatory effect. Patients with Kawasaki disease should be treated with a single 12-hour immunoglobulin infusion whereby 2 g/kg in a single infusion, together with aspirin, is administered in the acute phase with fever, or during the periods where inflammation progresses without fever. This therapy should be carried out within 7-10 days of the onset of the illness. With the benefit of high-dose IVIG treatment for acute-stage KD patients being widely recognized there has been a spike in its therapeutic use whereby IVIG accounts for 85% of pediatric patients with acute-stage KD being administered with the compound. The introduction of IVIG 10 days post onset of symptoms is not rooted, therefore, it is advised to start IVIG therapy as soon as possible.

**Aspirin**

Aspirin was the first drug used for the treatment of KD, owing to its anti-inflammatory and anti platelet aggregating effects. In light of the possible risks of aspirin, it should be withheld in the presence of bleeding, exposure to influenza or varicella, or in patients with a history of hypersensitivity to salicylates. 100 mg/kg/d is usually the initial dose and not any higher. Aspirin at a high dose is initially used for its anti-inflammatory effect, but in the post-acute phase of Kawasaki disease, the dose of aspirin is reduced to 5 mg/kg/day which acts as an inhibitor of platelet activity. This treatment persists for 6 weeks if there are no signs of coronary artery abnormalities or longer if the coronary arteries remain abnormal.

**Adjuvant Therapy and Treatment Options for Cases Refractory to IVIG and ASA**

**Corticosteroids**
Intravenous methylprednisolone pulse remains the steroid of choice which is usually followed by oral prednisolone dose tapering. Studies were carried out on the pharmacologic efficiency of a single dose of IV methylprednisolone but they did not demonstrate the same benefit of decreasing the incidence rate of coronary artery lesions when compared to studies that utilized moderate to high doses, i.e. 1–6 mg/kg/day prednisolone equivalent doses, over an extended course, more than 3 days. The latest AHA guidelines note that a longer corticosteroid treatment course may be considered in high-risk patients as primary adjunctive therapy or in patients resistant to IVIG.

Other therapies
Other immunosuppressive medications such as cyclosporine, cyclophosphamide, methotrexate, and plasma exchange, have on occasion been used in unresponsive patients to IVIG, steroids, and anti-TNFα. The use of these agents is not a routine recommendation but can be considered on a case-by-case basis post-physician specialist consultation. A Phase III, randomized, double-blind, placebo-controlled trial explored infliximab’s use as a primary treatment for KD coupled with IVIG. The patients undergoing this trial experienced fast fever resolution and rapid improvement of inflammation markers without adverse effects. Inasmuch as this, this form of therapy is now very rarely used.

Conclusion
Due to the increased mortality rate of Kawasaki disease in pediatric patients, it is therefore imperative to acknowledge the long-term cardiovascular complications that may be experienced by patients with Kawasaki Disease. Moreover, owing to the relative uncertainty of this disease pathogenesis, more critical research needs to be developed to develop concise and more accurate diagnostic tests in determining the extent of disease occurrence in a patient population. A push to develop a global treatment guideline would certainly be invaluable in curbing the mortality rates among pediatric patients.

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Points to Remember:
- Kawasaki is more prevalent in children than adults and the symptoms experienced in children are more extreme
- Being the second most common Vasculitis illness in children, proper diagnosis and care should be carried out before further development of the disease.
- Due to no precise diagnostic tests existing, fever lasting for more than 5 days should be seen as a possible precursor to the Kawasaki disease and symptoms should be compared alongside a host of possible criteria points to ensure if the illness is present or not.
- A combination of intravenous aspirin and an immunoglobulin is seen as a mainstay in treating this disease
- Immunosuppressant use can be used in patients experiencing unresponsiveness to immunoglobulin therapy.

Reference