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KAWASAKI SYNDROME- A REVIEW

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ABSTRACT: Aim: The aim of this review is to provide a detailed documentation and main features such as prevalance, manifestations and management regarding Kawasaki syndrome. **Background**: Kawasaki Syndrome was first described by Dr Tomisaku Kawasaki in Japan in 1967, since then prevalence of Kawasaki syndrome is increasing in all countries as per the reports in journals. This is more prevalent in Asian pacific regions. Kawasaki Syndrome is the most common cause of acquired heart disease in the U.S. and Japan with a high endemic rate of 150 per 100,000 in children less than 5 years. **Materials and methods:** This is a review based article, thus information regarding the topic was collected from different journals like European journal of paediatrics, Indian paediatrics , AHA scientific council etc. **Reason:** The purpose of this review is to put forward a well explained article about Kawasaki syndrome.

INTRODUCTION: Kawasaki syndrome or Kawasaki disease is a systemic necrotising vasculitis affecting the medium and small sized arteries [1, 2]. It is not only the commonest vasculitic disorder of children, but is also the commonest cause of acquired heart disease in children in many countries [1, 3, 4]. It primarily affects infants and young children, with 80-85% of the subjects being below 4 years of age [1, 4, 5]. Boys are affected more commonly than girls and there is an ethnic bias in favour of children of Asian (specially Japanese and Korean) and Afro- Caribbean extraction [1, 2, 4, 5]. Kawasaki syndrome is an autoimmune disease [6] in which the medium-sized blood vessels throughout the body become inflamed. It is largely seen in children under five years of age.

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It affects many organ systems, mainly those including the blood vessels, skin, mucous membranes, and lymph nodes. Its rarest but most serious effect is on the heart, where it can cause fatal coronary artery aneurysms in untreated children. Without treatment, mortality may approach 1%, usually within six weeks of onset. With treatment, the mortality rate is 0.17% in the U.S [7].

The other common synonyms of kawasaki syndrome are Kawasaki disease, lymph node syndrome, mucocutaneous lymph node syndrome [8]. Often, a pre-existing viral infection may play a role in its pathogenesis [9]. The skin, the conjunctivae of the eyes, and the mucous membranes of the mouth become red and inflamed. Swelling of the hands and feet is often seen and lymph nodes in the neck are often enlarged. A recurrent fever, often 37.8 °C (100.0 °F) or higher, is characteristic of the acute phase of the disease [10]. In untreated children, the fever lasts about 10 days, but may range from five to 25 days [10].

History: Kawasaki syndrome was first described by Tomisaku Kawasaki in 1967 when he reported 50 children who had presented with a distinctive clinical illness and to which he gave the name `acute febrile mucocutaneous lymph node syndrome [11]. Soon thereafter, Marian Melish independently reported children with a similar clinical profile from Hawaii in the United States. KD has now been reported from all parts of the world, including several centres in India. Based on the epidemiology and clinical features, an infectious etiology has been suspected for long but no definitive causative agent has been implicated so far. Like many other vasculitides, the diagnosis of this condition is based on the recognition of a temporal sequence of clinical features, none of which is pathognomonic in isolation. It was initially thought to be a self-limiting benign illness, but by 1970 ten fatal cases had been reported out of which 4 had evidence of coronary artery aneurysms with thrombosis [5]. Kawasaki Disease (KD) has now been described from all parts of the world and in all races [1, 3, 4, 5]. However, till very recently, reports from India had been few and far between[12-19].

Incidence rates as high as 60-150 per 100,000 children below 5 years of age have been reported from several countries. In India (as also perhaps in many other developing countries), however, majority of children with KD continue to remain undiagnosed probably because of the lack of awareness amongst paediatricians. The clinical features of KD can be confused with other common conditions like measles fever, scarlet fever and the Stevens Johnson syndrome etc, if the clinician is not careful. Development of coronary artery abnormalities (CAA) is the hallmark of KD and accounts for most of the morbidity and mortality associated with the disease. Prompt recognition of the disease and early initiation of treatment with intravenous immunoglobulin (IVIG) results in significant reduction in the occurrence of CAA. It is, therefore, imperative for the paediatrician to diagnose and treat KD expeditiously. KD should be considered in the differential diagnosis of all febrile illnesses in young children where the fever persists for more than 5-7days [20].

Epidemiology: Kawasaki disease affects boys more than girls, with people of Asian ethnicity, particularly Japanese and Korean people, most susceptible, as well as people of Afro-Caribbean ethnicity. The disease was rare in Caucasians until the last few decades, and incidence rates fluctuate from country to country.

Currently, Kawasaki disease is the most commonly diagnosed paediatric vasculitis in the world. By far, the highest incidence of Kawasaki disease occurs in Japan, with the most recent study placing the attack rate at 218.6 per 100,000 children <5 years of age (about one in 450 children). At this present attack rate, more than one in 150 children in Japan will develop Kawasaki disease during their lifetimes.

However, its incidence in the United States is increasing. Kawasaki disease is predominantly a disease of young children, with 80% of patients younger than five years of age. About 2,000-4,000 cases are identified in the U.S. each year (9 to 19 per 100,000 children younger than 5 years of age [21, 22, 23].

In the United Kingdom, estimates of incidence rate vary because of the rarity of Kawasaki disease. However, it is believed to affect fewer than one in every 25,000 people [24]. Incidence of the disease doubled from 1991 to 2000, however, with four cases per 100,000 children in 1991 compared with a rise of eight cases per 100,000 in 2000 [25].

Causes: The etiology remains an enigma [5, 26, 27, 28]. The profile of clinical features (e.g. febrile exanthema, conjunctival injection, cervical adenitis) is very reminiscent of an infectious etiology [5, 26]. The age profile of the disease (rarely seen in very young infants and adults) also suggests an infectious process [29, 30]. Similarly the fact that the disease has been known to occur in epidemics (as documented from Japan) is a strong pointer towards an infectious process [5, 27, 30]. However, conventional bacterial and viral cultures have so far been singularly unrewarding. Serologic investigations have also not yielded any definitive clues towards an infectious cause [28, 31].

Expression of Vb T-cell receptor families in peripheral blood T cells in patients with acute KD has been the focus of several investigators. The results are, however, equivocal. Similarly the role of staphylococcal and streptococcal super antigens (such as toxic shock syndrome toxin-1), in the etiopathogenesis of KD has been under close

scrutiny, especially because some of the clinical features of KD (eg. exanthema and peripheral desquamation) are reminiscent of a toxic shock syndrome [32].

Recent studies by Onouchi, et al. [28] suggest that a common infectious agent that triggers clinically apparent disease in certain genetically predisposed individuals, particularly Asians, causes KD. The precise genetic factors conferring susceptibility to KD are, however, unknown.

The basic pathological lesion is a pan-arteritis affecting medium sized vessels, principally the coronaries [5, 27, 33]. In the acute phase, widespread inflammation may be seen in various organs like the heart, meninges, lungs, lymph nodes, and liver. Initially, polymorphonuclear infiltration is seen in vessel walls and mononuclear cells soon replace this. During recovery, inflammation subsides but leaves behind fibrous connective tissue in the vessel wall along with proliferation of intima. This process is most pronounced in coronary arteries, where aneurysms can form during the subacute phase [5, 27, 35]. Because of vessel wall damage,

patients are prone to develop thrombosis later in life leading to myocardial ischemia, myocardial infarction and sudden death. It should be noted that ischemic events in the heart can occur months to years after the acute event. Adult onset ischemic heart disease as a result of KD in childhood is a well recognised entity [5, 35].

Hamashima and Fujiwara [36] classified the course of angitis into 4 stages according to the duration of illness.

- Stage one is one to two weeks from onset.
- Stage two is two to four weeks from onset.
- Stage three is four to seven weeks from onset.
- Stage four is more than seven weeks from onset.

Major causes of death in each stage are as follows:
In stage one, the major cause is myocarditis, including inflammation of the AV conduction system. In stages two and three the major causes are ischemic heart disease, rupture of aneurysms and myocarditis. In stage four the major cause is ischemic heart disease.

It is, therefore, apparent that KD may not be only a one time disease of childhood. The sequelae associated with the disease mandate long term follow-up of affected children.

Diagnosis: The diagnosis of KD is difficult because it is based entirely on the recognition of a typical temporal sequence of a constellation of clinical features, with none of the features taken individually being of any diagnostic significance [4, 5]. There is no laboratory test which can help the clinician in arriving at or confirming a diagnosis of KD [4, 5]. The difficulty is further compounded by the fact that the clinical features gradually evolve over a period of days to a few weeks, and the entire clinical spectrum is not seen at any one particular point of time. Moreover, it may be difficult to distinguish KD from other common febrile illnesses of childhood [4, 37]. Early diagnosis, however, is imperative in order to avoid the risk of acute coronary vasculitis which can occur in up to 30% of cases and which can be minimised by prompt administration of intravenous immunoglobulin therapy [38-43]. In the absence of a specific diagnostic test for Kawasaki syndrome,clinical criteria have been established to assist the physician in making the diagnosis [44].

Principle symptoms for the diagnosis of kawasaki syndrome:

1. Fever for at least 5 days in duration.
2. Presence of any four* of the following 5 characteristics:

- Changes in extremities
- Polymorphous exanthema
- Bilateral conjunctival injection
- Changes in the lips and oral cavity
- Cervical lymphadenopathy

3. Exclusion of other diseases with similar findings.
The clinical profile of KD can be divided into the following three phases [5, 27, 34, 45].

1. Acute phase (0-10 days): High grade fever (unresponsive to antimicrobials), extreme irritability (often out of proportion to the degree of fever) and bilateral conjunctival injection are the usual presenting features and are characteristic of the early phase of KD. Most of the other features mentioned in the diagnostic criteria are also seen during this phase.

Myocarditis is common at this time but may not be clinically discernible. An experienced paediatrician should be able to make the diagnosis in the first few days of the illness. Administration of intravenous immunoglobulin is most beneficial when given in the first 10-12 days of the fever.

2. Subacute phase (10-28 days): This phase corresponds to the period when most of the clinical features seen in the acute stage are subsiding. One clinical feature that is typically seen during this time is periungual desquamation. CAA demonstrable on echocardiography are also first seen at this time. Thrombocytosis is sometimes very prominent and this finding in presence of periungual desquamation is said to be virtually pathognomonic of KD. Though clinical diagnosis is relatively easy in this phase, the paediatrician should endeavour to establish the diagnosis much earlier. There is a risk of sudden death in this phase, though we have never encountered it in our practice.

3. Convalescent phase: Begins when all clinical signs have disappeared and continues till the acute phase parameters (e.g. elevated C-reactive protein, thrombocytosis, erythrocyte sedimentation rate) return to normal. This usually occurs by the end of 6- 8 weeks after the onset of the illness. Erythema of the palms and soles and/or firm, sometimes painful in duration of the hands or feet often occurs in the early phase of the disease. Desquamation of the fingers and toes usually begins 1-3weeks after onset of fever in the periungual region and may extend to include the palms and soles. Approximately1-2months after the onset of fever, deep transverse grooves across the nails (Beau's lines) may appear.

A polymorphous exanthema usually appears within 5 days of the onset of fever. The rash may take various forms, including an urticarial exanthema, a maculopapular morbilliform eruption, a scarlatiniform erythroderma, an erythema multiform like rash, or, rarely, a fine micro pustular eruption. Bulbous eruptions have not been described. The rash is usually extensive with involvement of the trunk and extremities and accentuation in the perineal region. Bilateral conjunctival injection usually begins shortly after the onset of fever. It typically involves the bulbar conjunctivae much more than the palpebral or tarsal conjunctivae, is not associated with an exudate, and is usually painless.

Changes of the lips and oral cavity include erythema and cracking of the lips, strawberry tongue, and erythema of the oropharyngeal mucosa. Oral or lingual ulcerations are not seen.

Cervical lymphadenopathy is considered a principal finding when at least one lymph node is more than1.5cm in diameter. The lymphadenopathy is generally unilateral and the nodes are usually firm and slightly tender. There may be some overlying erythema but the nodes are non fluctuant. Among the five principal clinical features, cervical lymphadenopathy is the least common.

Because the principal clinical findings to fulfil the diagnostic criteria are not specific, other diseases with similar clinical features should be excluded. Consideration of measles as a possible diagnosis is particularly important because cases have been mis diagnosed as Kawasaki disease and appropriate control measures have not been taken promptly.

Treatment: Once a diagnosis of KD has been made the treatment is quite straightforward. Intravenous immunoglobulin (IVIG) given either as a single bolus of 2 g/kg or as 400 mg/kg infusion daily for 4 days, results in prompt resolution of fever and irritability[1, 3, 45, 46].

Intravenous immunoglobulin (IVIG) is the standard treatment for Kawasaki disease and is administered in high doses with marked improvement usually noted within 24 hours. If the fever does not respond, an additional dose may have to be considered. In rare cases, a third dose may be given to the child. IVIG by itself is most useful within the first seven days of onset of fever, in terms of preventing coronary artery aneurysm.

Aspirin is given at 100 mg/kg/day for the first 2 weeks and thereafter in doses of 3-5 mg/kg/day. Aspirin is continued till the ESR and platelet counts return to normal and this usually takes 4-6 weeks. If coronary aneurysms have developed, aspirin may need to be continued indefinitely. Unlike all other vasculitides, steroids are contraindicated in KD [1, 4, 5].

IVIG suppresses the formation of coronary aneurysms, improves myocardial perfusion and reverses lymphocyte activation [3, 31, 47]. The mechanism of action is through down regulation of cytokine production, blockage of Fc receptors and suppression of antibody function through the anti-idiotypic pathway [2, 3, 4].

For the paediatrician it is of the utmost importance to diagnose KD in the acute stage because as many as 20-30% of untreated patients may develop coronary artery abnormalities [32]. With treatment this figure can be brought down to as low as 1-2% [2-5]. In the first 10 days there may be evidence of myocarditis, pericarditis or arrhythmias. In fact myocarditis occurs in virtually all patients with KD and can be demonstrated by specialised scanning techniques. The coronary arteritis which occurs during this period evolves into coronary artery aneurysms which are first seen from 10-28 days after the onset of illness [1, 3, 5]. Such aneurysms usually do not develop after the first 4 weeks of illness. Death can result from acute myocarditis, arrhythmias, myocardial infarction secondary to thrombosis of an aneurysm or from rupture of an affected coronary artery.

The long term outcome depends on degree of cardiac involvement and the maximal luminal diameter of the affected coronary artery. There have been several reports of myocardial infarction, premature onset ischemic heart disease, juvenile onset atherosclerosis and sudden death occurring many years after an episode of KD [48-51]. As a corollary one should try and look for a clinical history of KD in the past in all young adults who present with myocardial infarction/ischemia, specially in those individuals who have no suggestive family history and risk factors for ischemic heart disease [50, 51].

CONCLUSION: Kawasaki syndrome is a common paediatric condition affecting young children and has been reported from all parts of the world, including several developing countries [5, 52-56]. This acute self- limited medium-vessel vasculitis has become the most common cause of acquired heart disease in children in the United States and Japan. It is our belief that in India at present, the overwhelming majority of children with Kawasaki syndrome is not being recognised and is consequently being denied therapy. For the paediatrician, it is important to diagnose as early as possible because 20-30% of untreated patients develop Coronary artery aneurysm. It is incumbent on us paediatricians to familiarise ourselves with the typical constellation of clinical features which constitute Kawasaki syndrome so that prompt therapy can be instituted and the devastating cardiac complications can be avoided.

CONFLICTS OF INTEREST: Nil.

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