

## Kawasaki Disease – An Indian Perspective

SURJIT SINGH AND \*TOMISAKU KAWASAKI

*From the Pediatric Allergy and Immunology Unit, Advanced Pediatric Center, PGIMER, Chandigarh, India; and \*Japan Kawasaki Disease Research Center, Chiyoda-Ku, Tokyo, Japan.*

*Correspondence to: Dr Surjit Singh, Professor of Pediatrics, Advanced Pediatric Center, Post Graduate Institute of Medical Education & Research, Chandigarh 160012, India. E-mail: surjitsinghpgi@rediffmail.com*

Kawasaki disease (KD) was first reported from Japan in 1967 by a young pediatrician, Tomisaku Kawasaki, while working at the Red Cross Hospital in Tokyo. 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 centers 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. KD is believed to be the commonest vasculitic disorder of children. 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 pediatricians. The clinical features of KD can be confused with other common conditions like scarlet fever and the Stevens Johnson syndrome, 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 pediatrician 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 5-7 days.

**Key words:** *Coronary artery abnormalities; India; Kawasaki disease.*

**K**awasaki disease (KD) is a medium vessel vasculitis affecting young children and presents as an acute febrile illness(1-3). It is characterized by the development of coronary artery abnormalities (CAA) in 15-25% of affected individuals that may lead to significant long term cardiac morbidity, if not diagnosed and treated in time(1-2).

KD was first reported by a Japanese pediatrician, Tomisaku Kawasaki, in 1967 in a Japanese language journal, *Arerugi*(1). He described 50 children who appeared to have a unique set of clinical features which he called the 'Mucocutaneous lymph node syndrome'(1-3). This was initially thought to be a benign clinical condition but soon it was realized that some children went on to develop coronary artery aneurysms. KD has now been described from all over the world(1-8).

The description of this new disease entity was initially met with lot of skepticism and opposition from pediatricians within Japan and it was not till the mid-1970s that the condition came to be accepted as a distinct new entity in its own right(2).

### IS KAWASAKI DISEASE COMMON IN CHILDREN?

KD is a common pediatric disorder with the annual incidence being in the range of 60-150 per 100,000 children below 5 years of age(1-3). It is the commonest pediatric vasculitis and also the commonest vasculitic disorder amongst all ages.

The misconception amongst many pediatricians in India that KD is uncommon, therefore, does not have any basis(9-11).

KD occurs worldwide and affects children of all races, although Asians are believed to be at highest

risk(1-4). Japan with a population of 128 million reports more than 5000 new cases every year(2,8). Our data at PGIMER, Chandigarh, suggest that the number of cases diagnosed to have KD has been showing a sustained increase since the mid-1990s, probably as a result of increased awareness amongst the referring physicians. Since 2004, KD has replaced Henoch-Schonlein purpura as the commonest vasculitic disorder amongst hospitalized children at our institute(12,13).

In many countries (including the United States and Japan), KD has now replaced acute rheumatic fever as the commonest cause of acquired heart disease in children(2-4,8).

#### **WHICH IS THE AGE GROUP AFFECTED?**

KD is a disease of young children with 80% of the patients being under the age of 5 years. While the peak age of onset of KD in Japan is 6 to 11 months, it is somewhat higher in the United States (*viz.* 18-24 months)(2,3,8). The condition is uncommon in infants below 3 months of age, but has been known to occur even in neonates(7). The male-to-female ratio is 1.5:1.0. Our data at Chandigarh are, however, somewhat different. We have found that almost 30% of our patients were above 5 years of age(8,12,13).

#### **IS THE DIAGNOSIS OF KD BEING MISSED IN INDIA?**

Till the late 1990s, there were only a handful of centers in India(12-20) that were regularly diagnosing and treating children with KD. The situation now is much better with several hospitals having developed expertise in the diagnosis and management of this condition. In spite of this, however, it is our firm belief that majority of children with KD in India are still not being diagnosed(9,10,12,13). There could be many reasons for this but perhaps the most important is the fact that most pediatricians (and physicians looking after children) in India are perhaps not fully conversant with the clinical manifestations of the disease during the acute phase(9,10,12).

#### **WHAT IS THE ETIOLOGY OF KD?**

The etiology remains an enigma(1-3,21). The profile of clinical features (e.g. febrile exanthema,

conjunctival injection, cervical adenitis) is very reminiscent of an infectious etiology(1,2). The age profile of the disease (rarely seen in very young infants and adults) also suggests an infectious process(7,8). 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(2,3,8). 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(21,22).

Expression of V $\beta$  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 superantigens (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. exanthem and peripheral desquamation) are reminiscent of a toxic shock syndrome(23).

Recent studies by Onouchi, *et al.*(21). 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.

#### **WHAT IS THE PATHOLOGY IN KD?**

The basic pathological lesion is a pan-arteritis affecting medium sized vessels, principally the coronaries(2,3,5). 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(2-4). The treating physician has to be aware of the sequence of these changes. It must be remembered that CAA are often not seen in the first 5-7 days of the

illness(2). An echocardiographic examination done very early in the disease can give an erroneous impression that there has been no coronary involvement, when in reality this may not be the case.

Because of vessel wall damage, these 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(24). Adult onset ischemic heart disease as a result of KD in childhood is a well recognized entity (2,24).

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.

#### HOW DOES ONE DIAGNOSE KD?

To the uninitiated, the diagnosis of KD may seem like an enigma. There seems to be more of “art” than “science” in arriving at a diagnosis(2-4, 25). KD remains purely a clinical diagnosis and is a delight for the hardcore clinician. It cannot be over-emphasized that the diagnosis rests 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 whatsoever. Moreover, these clinical features may change from day to day, the spectrum evolves over a period of time (1-3 weeks) and the entire clinical spectrum is not seen at any one particular point of time. There is no laboratory test or marker which is pathognomonic of the condition. Diagnosis of KD can be very challenging in certain situations(26).

In view of the rapidly changing clinical picture seen in KD, it has been our practice to hospitalize all children referred with a suspected diagnosis of KD so that these evolving clinical features can be closely observed and recognized and treatment initiated in time, if required(10,12).

In the absence of a specific laboratory test for KD, a set of clinical criteria have been established to assist the physician in arriving at a diagnosis(2,3,26)

(**Table I**). Needless to say, the sensitivity and specificity of these criteria has not been worked out. For a given patient an experienced clinician may be justified in making a diagnosis of KD even when all the criteria are not being met.

#### HOW DOES KD PRESENT TO THE CLINICIAN?

The clinical profile of KD can be divided into the following three phases(2-4, 26)

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 pediatrician 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

**TABLE I** DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE

1. Fever of at least five days duration.
2. Presence of any four\* of the following 5 features:
  - 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

\*Patients with fever and fewer than four principal clinical features can be diagnosed as having Kawasaki disease when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography.

clinical diagnosis is relatively easy in this phase, the pediatrician 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.

## WHAT ARE THE USUAL CLINICAL FEATURES?

### 1. Fever

Fever is usually the main presenting complaint in children with KD and the pediatrician must consider this condition in the differential diagnosis of all children with fever persisting for more than 5-7 days. In patients with KD, the fever is generally high-spiking (usually  $\geq 39^{\circ}\text{C}$ ) and remittent. It persists for 1 to 2 weeks in the absence of treatment but may well continue for 3 to 4 weeks. From the clinician's point of view, it is important to remember that this fever is not associated with the typical features of an upper respiratory catarrh (for *e.g.* conjunctivitis, rhinitis) – *i.e.* it is a 'dry fever'. This fever responds promptly to administration of intravenous immunoglobulin(2,26).

### 2. Conjunctival injection

Conjunctival injection in patients with KD usually begins shortly after the onset of fever, is nonexudative and is quite distinctive with bulbar conjunctivae being much more affected than the palpebral conjunctivae. A perilimbal sparing (usually 1-2 mm) is often seen. Most treated patients have prompt resolution of the conjunctival injection, although mild injection may persist for 1 to 2 weeks. Anterior uveitis may be present at this time but it requires a slit-lamp examination for confirmation. Uveitis has not been a common finding in our experience.

### 3. Mucosal changes

Mucosal changes include a characteristic redness of the mouth and lips with dryness and fissuring,

peeling of the lips and a typical 'strawberry tongue'. In our experience, the most prominent of the aforementioned findings is erythema of the lips which is seen in the first few days of the illness.

### 4. Changes in the periphery

Changes in the hands and feet include redness of the palms and soles often accompanied by a characteristic 'indurative edema' on the dorsal aspects. This is almost pathognomonic of KD. These changes are, however, only seen in the acute phase and may have completely disappeared by the end of the second week. These peripheral changes are followed by a typical periungual desquamation of fingers and toes in the subacute stage of the illness. One to two months after the onset of KD, transverse ridged grooves may develop across the base of the nails (Beau's lines) and grow out with the nail. Beau's lines comprise the only clinical finding of KD that can be seen for several weeks(2,26).

### 5. Rashes

The rash can be very variable. A diffuse nonspecific maculopapular erythematous rash is the most common, often with a 'perineal accentuation'. However, a scarlatiniform rash and an erythema multiforme-like rash with target lesions has also been described. The latter can be confused with the Stevens Johnson syndrome. In our experience, many of these rashes may be erroneously labelled as 'drug rashes', thereby resulting in diagnostic confusion. It is noteworthy that a vesicular rash is never seen in KD. The rash of KD may be almost inapparent in children with dark complexions, unless looked for carefully. We have often faced this difficulty.

### 6. Cervical lymphadenopathy

Cervical lymphadenopathy is also quite variable. It is seen in only 50-75% of patients, whereas most of the other features are seen in approximately 90%. Occasionally, massive cervical node enlargement may be the presenting clinical feature of KD and we have one such patient on our records. It is an axiom that KD should be thought of in all children with a febrile unilateral acute cervical adenitis, especially when it is unresponsive to antimicrobials(2,26).

### WHAT ARE THE FEATURES CONTRIBUTING TO DIAGNOSTIC CONFUSION IN KD?

Like many of the other vasculitides, KD is a multisystemic disorder and this can make clinical decision making rather difficult, especially for the uninitiated(2,10,12,13,26). With some experience, however, it is not difficult to recognize the characteristic constellation of clinical findings and arrive at a diagnosis of KD. This constellation can be so typical as to preclude any differential diagnosis whatsoever. Extreme irritability (out of proportion to the degree of fever) is particularly common in young infants with KD.

Diagnostic confusion can undoubtedly arise in several patients. For instance, about one fourth of KD patients have associated aseptic meningitis and the cerebrospinal fluid changes of KD can be confused with a meningitic illness. Similarly, the arthritis commonly associated with KD can be mistaken for a primary joint disease. We have seen this happen on more than one occasion. Mild elevations of serum bilirubin and transaminases can occur in many patients during the acute phase of KD(2-4,26). This can be mistaken for a viral hepatitis. Acute distension of the gallbladder (hydrops) can also occur in KD and contribute to the woes of the attending physician if one is not careful!

### WHAT IS ATYPICAL KD?

When a patient has clinical features not commonly associated with this condition, a diagnosis of “atypical” KD can be made(2,3,26). For instance, the presence of significant hypertension, nephritis, seizures or a cerebrovascular accident in a patient with KD would be distinctly atypical. Needless to say it may be extremely difficult to make a correct diagnosis of this condition under such circumstances(2,3,26-30).

### WHAT IS INCOMPLETE KD?

Children presenting with fever and fewer than four of the other clinical features are said to have “incomplete” KD. Children with incomplete KD also have a significant risk of CAA. We have also reported one such patient(30). Atypical KD is believed to be more common in young infants and

clinical recognition of such cases can sometimes be quite difficult(2,3,26-30).

### WHAT ARE THE LABORATORY FINDINGS IN KD?

KD is essentially a clinical diagnosis and there are no laboratory tests that are pathognomonic of KD. In fact some laboratory abnormalities seen in KD may lead the clinician away from the diagnosis. For instance, pyuria is a common finding in KD but can be easily mistaken for a urinary tract infection during the febrile phase of KD(2,3,26).

Other laboratory findings, however, may point towards a diagnosis of KD. A polymorphonuclear leucocytosis is typically seen in the acute phase. Elevations in erythrocyte sedimentation rate and the C-reactive protein are almost universally present in the first week of illness and may persist thereafter for 4 to 6 weeks. Normocytic anemia is common in patients with acute KD and is more severe in patients with a prolonged febrile stage or who develop coronary disease. The platelet count is generally normal in the first few days of the illness but counts in excess of  $1 \times 10^6$ /cu mm can be seen after the second week(2,3,25). This thrombocytosis is rather characteristic of KD, but is usually not there to help the clinician in the crucial first 7-10 days of fever when administration of IVIG is most useful. Echocardiography is used for detection of CAA and in experienced hands has a sensitivity and specificity of more than 95%. It must be noted that echocardiography can be completely normal in the first week of illness as the coronary artery changes take some time to evolve(2,3,26).

### WHAT ARE THE CARDIOVASCULAR MANIFESTATIONS OF KD?

KD can be associated with significant cardiac sequelae. CAA are seen in approximately 15% to 25% of untreated KD patients. These can take the form of diffuse dilatation (ectasia) and aneurysm formation(2,3, 26, 31-33). CAA can be diagnosed by echocardiography after the first week of illness. Appearance of new aneurysms more than 6 weeks after the onset of illness is, however, uncommon.

The fate of coronary aneurysms due to KD has been prospectively studied by Kato, *et al.* in

Japan(31,32). Majority of the aneurysms regress or show a decrease in size over the next few months. Patients who do not have complete resolution of aneurysms may go on develop coronary stenosis. This coronary stenosis is a dreaded complication and may be complicated by premature atherosclerosis and lead to significant coronary obstruction and myocardial ischemia later in life. These ischemic events may be virtually indistinguishable from those seen in association with primary atherosclerosis.

Aneurysms larger than 8 mm in diameter (giant aneurysms) can be seen in a small minority of patients with KD and often do not regress(2,3,26). Stenosis or complete obstruction occurs in half of these and may result in significant morbidity/mortality.

Kato, *et al.*(31) have also shown that in patients with persistent aneurysms, coronary artery stenosis can develop many years after the acute episode of KD. Myocardial infarction occurred in 1.9% of all the KD patients and in as many as 39% of those having persistent aneurysms. Majority of myocardial infarctions develop within 1 year of the onset of KD and the mortality rate in such cases can go up to 20%(32).

Certain clinical factors are predictive of an increased risk for coronary disease – these include prolonged fever, recurrence of fever following an afebrile period of more than 48 hours, arrhythmias other than first-degree heart block, male gender, age less than 1 year and cardiomegaly(2,3,26).

KD is said to be the commonest cause of myocardial infarction in children. Myocardial infarction in children presents with atypical symptoms as compared to adults. A review of 195 cases of myocardial infarction caused by KD in Japan indicated that as many as 37% of infarcts were asymptomatic(2,3,32). The main presenting complaints were uneasiness, vomiting, shock and abdominal pain. These symptoms can be easily mistaken for other childhood illnesses. Of note, chest pain may not be a significant feature in young children. Further, in 63% of children, the attack occurred during sleep or at rest. However, the electrocardiogram and cardiac enzyme changes are like those in adults.

Although coronary aneurysms are the most significant cardiovascular complication of KD, other cardiac complications can also occur(26,34). These include myocarditis (some degree of which is believed to occur in all patients with KD), valvulitis (usually mitral), pericardial effusion and development of aneurysms in the systemic arteries. Myocarditis may manifest as tachycardia out of proportion to the degree of fever. Electrocardiographic abnormalities such as prolonged PR interval, ST-T segment changes and decreased voltage of R waves may also be suggestive of myocarditis. Pericarditis with small pericardial effusions occurs in approximately 25% of acute KD patients. Valvular disease, predominantly mitral regurgitation, occurs in approximately 1%(2,3,26).

#### **CARDIOVASCULAR MANIFESTATIONS OF KD IN THE INDIAN CONTEXT**

It is our contention that as KD is not being diagnosed frequently in children in India, majority of the affected patients are at present being left untreated, thereby rendering them liable to coronary complications later in life(10,12). It is entirely possible that this cohort of untreated children with KD would grow up to develop coronary artery disease (CAD) as young adults(33-36). These untreated children may, therefore, be contributing to the total load of coronary disease encountered by our adult cardiologists. As a corollary, some of the young adults with myocardial infarction in our country, who have no risk factors for CAD and no family history either of a similar ailment, could be representing such untreated children with KD.

#### **TREATMENT OF KD**

##### ***Therapy in acute phase***

While the diagnosis of KD may pose significant problems for the attending physician, treatment is relatively straightforward(2,3,26). Intravenous immunoglobulin (IVIG) is very effective when given in the first 10 days of illness. It reduces the chances of development of CAA from 20-25% to 1-2% (36-42). With administration of IVIG, the irritability promptly disappears, there is a rapid defervescence of fever and normalization of the acute phase

reactants. IVIG also improves myocardial function in KD patients having myocarditis(43).

The optimal dose of IVIG in patients with KD is unknown but a strong inverse relationship exists between IVIG dose and prevalence of late coronary abnormalities(44). The preferred regimen is a single dose of 2 g/kg(2,3,26). It should be noted that till very recently some Japanese workers have been using a much lower dose of IVIG for treatment of KD(2). The mechanism of action of IVIG in patients with KD is unknown but may be related to the downregulation of the cytokine cascade.

Patients who present in subacute phase and have been afebrile for many days are usually not given IVIG, as it is unlikely to prevent coronary disease after the acute inflammatory response has subsided. In such patients it is our practice to consider IVIG treatment only if the patient continues to have fever(10,12).

Approximately 10% of KD patients may not respond to IVIG and continue to have persistent fever even 48 hours after administration of the drug(2,3,26). Such patients are said to have resistant disease and may require additional (one or two) doses of IVIG. Intravenous methylprednisolone can also be considered in such cases. Recently, the tumor necrosis factor alpha (TNF $\alpha$ ) antagonist, infliximab, has been recommended for use in such children.

Aspirin is administered in patients with KD for its anti-inflammatory and antithrombotic effects(2,3). During the acute phase of illness, aspirin is administered at 70-80 mg/kg/d given every 6 hours. Somewhat lower aspirin doses (30-50 mg/kg/day) have been used in Japan(2). Around the 14<sup>th</sup> day of illness, when fever has resolved, aspirin is reduced to antithrombotic doses of 3 to 5 mg/kg/day as a single daily dose which is then continued for the next few weeks.

Administration of parenteral virus vaccines (i.e., measles, mumps, rubella, and varicella) should be delayed for at least 3 months after IVIG because passively acquired antibodies may interfere with effective immunization. Schedules for administration of other routine childhood vaccinations need not be interrupted.

### *Therapy after the acute phase*

A repeat echocardiogram is obtained at 2-3 weeks and again at 6-8 weeks following the onset of illness. Aspirin can be discontinued after the sedimentation rate and platelet counts have normalized (this usually takes 6-8 weeks) and the echocardiograms are reported to be normal. If echocardiography done at 6-8 weeks reveals CAA, low dose aspirin should not be discontinued.

Further management of KD patients with aneurysms is dependent on the severity of coronary disease. Patients with a single small aneurysm should receive long-term aspirin and avoid physical sports. Patients with giant/multiple aneurysms need to be put on long-term anticoagulation.

### **MORTALITY ASSOCIATED WITH KD**

KD was associated with a mortality rate of 1-2% in the pre-IVIG era. With improved recognition and appropriate therapy of the disease in the acute phase, this has dropped to 0.08%. Deaths are most common 2 to 12 weeks after the onset of the illness and are usually secondary to the coronary aneurysms and complications thereof(2,3).

### **EPILOGUE**

KD is a common pediatric condition affecting young children and has been reported from all parts of the world, including several developing countries(2,10,12,45-47). Clinical and epidemiological features of KD support an infectious cause, but the precise etiology remains elusive. 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 KD is not being recognized and is consequently being denied therapy. This is unfortunate and unacceptable. KD can have significant sequelae in the coronary arteries that may lead to myocardial infarction and sudden death. Some of these sequelae can manifest years or decades after the acute event. For the pediatrician, it is important to diagnose KD as early as possible because 20-30% of untreated patients develop CAA. For the cardiologist, it is important to realize that

some of the so-called ‘coronary artery disease in the young’ may possibly represent sequelae of undiagnosed and consequently untreated KD in childhood.

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