SPECIAL ARTICLE

Kawasaki Disease in India – Lessons Learnt Over the Last 20 Years

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Over the last 20 years, Kawasaki disease is being increasingly recognized in India and it may soon replace acute rheumatic fever to become the commonest cause of acquired heart disease amongst children. However, the vast majority of children with Kawasaki disease in India are still not being diagnosed. Diagnosis of Kawasaki disease is based on a constellation of clinical findings which have a typical temporal sequence. All pediatricians must we familiar with the nuances involved in arriving at a diagnosis of Kawasaki disease. With early diagnosis and prompt treatment, the risk of coronary artery abnormalities can be significantly reduced.

Keywords: *Coronary artery aneurysm, Immunoglobulin therapy, Vasculitis*.

Kawasaki disease (KD) is a medium vessel vasculitis of young children with a special predilection for the coronary arteries [1-3]. KD is not only the commonest pediatric vasculitis but also the commonest vasculitis across all ages. In fact, KD would easily outnumber all the adult vasculitides put together [4-6]. No paediatrician can, therefore, afford to remain innocent about the nuances involved in diagnosis of this condition.

Children with KD present acutely with fever and a typical constellation of sequential clinical findings. Taken individually, none of these clinical findings is, by itself, diagnostic. Rather, it is the recognition of this constellation which leads one to the diagnosis. KD is a medical urgency – if not diagnosed and treated in time, approximately 15-25% of affected patients can develop coronary artery abnormalities (CAA), the sequelae of which may be long-lasting and devastating [1-3].

EPIDEMIOLOGY

Recent epidemiologic data [6] show that the incidence of KD in Japan is now 265/100,000 under-five children – the highest figure ever reported for KD. It is estimated that approximately 1% of children born in Japan would develop KD by the time they reach 10 years of age. Korea reports an incidence figure of 134.4 (second highest in the world) while Taiwan reports 82.8 (third highest in the world) per 100,000 under-five children [4-6]. Not only do these three countries have the highest incidence rates in the world, the incidence is also continuing to increase. For instance in Japan, the incidence of KD has doubled over the last 20 years. It is still not clear when, or whether, this incidence rate would stabilize or plateau [5]. Incidence rates in Europe and North America are much lower, and vary between 4 to 30/100,000 under-five children. Further, the incidence rates in these countries have plateaued, and have not shown a discernible increase over the last two decades [4-6].

KD has replaced rheumatic fever to become the commonest cause of acquired heart disease amongst children in Japan, Northern America and Europe [1-3]. Although we do not have countrywide epidemiologic data for India, anecdotal reports strongly suggest that the incidence (or at least ascertainment) of KD is showing an upward trend. For instance, extrapolations from the hospital-based registry at Chandigarh showed that the incidence of KD had increased from 0.51 to 4.54/100,000 children aged below 15 years during the period 1994-2007 [7]. At the same time, the incidence of rheumatic fever in India has been showing a gradually decreasing trend [8]. It is, therefore, entirely possible that KD may soon replace–or may have already replaced – rheumatic fever as the commonest acquired pediatric cardiac disorder in India.

In several countries, the emergence of KD has been linked to industrialization and the resultant increased economic growth and productivity [9]. Similar has been the case for India as well wherein the increased incidence of KD seems to have followed the opening up of the Indian economy in the early 1990s, and the consequent improvement in the socioeconomic status of the

population. In a recent prospective study from Chandigarh, it was found that the socioeconomic status of families of children with KD was higher than that of controls [10]. However, as countrywide data are not available, it would be imprudent to conclusively say that the emergence of KD has a direct association with affluence.

EMERGENCE OF KD IN INDIA

1991-1995

KD was not reported frequently from India till the mid-1990s. There were only 3 case reports of KD from India prior to 1990 [11-13]. One of the authors (TK) recalls an incident at the Asian Congress of Pediatrics which was held at New Delhi in 1994. In a session on pediatric vasculitis, I (TK) asked the chairperson how common was KD in this country. I was told in no uncertain terms that this condition does not occur in India! At that time I could not understand why this should be so, especially because KD had started being reported from all parts of the world, including several countries in South East Asia. That a country as populous as India should not be seeing KD looked incongruous to me. My disappointment was, fortunately, short lived as events in the latter half of that decade were to show later [14-16].

1996-2000

In the year 1997, *Indian Pediatrics* published two case series on KD, one each from Thiruvanthapuram and Chandigarh [15,16]. While the two centers had been seeing cases with KD at regular intervals, they were unaware of each other's work. These two series on KD were followed by several reports from other parts of the country [17-19].

It was around this time that KD gradually started being discussed at various pediatric fora including annual conferences of Indian Academy of Pediatrics. Though many pediatricians had begun diagnosing and treating KD in India, there was no dearth of sceptics who vociferously, and at times, aggressively challenged the diagnosis. The lead author (SS) can recall several national conferences and meetings wherein these debates, often heated, took place. The proponents of KD often had to face ridicule, criticism and sarcasm at these meetings. To add to our woes, there was also the dilemma of 'incomplete' and 'atypical' KD – clinical entities which appeared very nebulous at that time.

Pediatricians in India, however, slowly came to terms with the myriad ways in which KD can manifest and realized that this enigmatic entity can have an expanded clinical spectrum of presentation. At this time, however, most pediatricians (including the lead author - SS) were only offering therapy to those children who had the classical forms of KD.

2001-2005

Gradually the pediatric fraternity in India accepted that KD is indeed a reality in the country, and that no pediatrician could afford to miss the diagnosis. In the year 2005, I (TK), along with my friend Dr. Hirohisa Kato, received an invitation from the Post Graduate Institute of Medical Education and Research in Chandigarh to deliver lectures at the Annual Conference of Rheumatology Chapter of Indian Academy of Pediatrics. We gladly accepted this invitation.

During our visit to India in October 2005, Dr. Kato and I had the opportunity to interact with a large number of pediatricians, internists, cardiologists and pediatric rheumatologists in New Delhi and Chandigarh. We came back convinced that KD in India was, at last, being given the importance that it deserved [20-22]. It was also heartening to note that many unusual presentations of KD were being identified. It was gratifying to note that KD as a 'spectrum of disease' was firmly established in the diagnostic armamentarium of pediatricians in India.

2006-2010

The increasing number of reports on KD from India over a short span of time was intriguing and attracted the attention of several other workers across the world. Dr. Jane Burns led a team of researchers from the Kawasaki Disease Research Centre in San Diego, USA and the Emory University, Atlanta, USA, and visited India in February 2006. She set up interviews with several centers that had been diagnosing and reporting KD. These interviews can even now be accessed at the website of the Kawasaki Disease Research Centre, San Diego.

The researchers wanted to know whether the emergence of KD in India represented a new disease that was hitherto non-existent or was it merely the increased ascertainment of an already existing disease as a result of increased awareness, or was it a combination of both factors. This dilemma, however, remained unresolved. While some senior pediatricians in India opined that in their clinical experience over several decades, they had never seen children with symptoms of KD, others felt that this disease had been missed hitherto because of lack of awareness. According to the latter viewpoint, KD in the past had probably been confused with other febrile exanthematous illnesses of childhood.

Burns, *et al*. [23-25] also noted that the phenotype of KD in India appeared to have some differences when

compared with Japan and North America. In India, children with KD were older with almost half of them being over the age of five years. This could be because of biological differences due to genetic heterogeneity amongst different populations. However, it is also possible that in India the diagnosis of KD is being missed in infants and young children in whom the condition is being confused with viral exanthemata. Further, Burns, *et al*. also noted a significantly greater male preponderance when compared with published data from Japan and North America. Periungual desquamation, which is so typical of KD, often appears prior to Day 10 of fever in India while it usually occurs a couple of days later in the developed countries. Similarly, thrombocytosis is seen earlier in India as compared to other countries [23-25].

During the period 2006-2010, one can also perceive a distinct consolidation phase of KD in the Indian literature [26-29]. Further, follow-up studies on children with KD made their appearance for the first time in Indian literature [30, 31]. The first KD Summit was organised in 2010 at Parumala, Kerala. This became a regular biennial event later. Chandigarh recently hosted the third KD Summit in October 2015 [32].

Hospital-based data from Chandigarh suggested that KD, and not Henoch Schonlein purpura, was the commonest pediatric vasculitis at that center [33]. The number of publications on KD from India also showed a quantum leap during this period. Pediatricians in India also started exploring other therapeutic options and the first reports on use of infliximab and methylprednisolone started appearing in the Indian literature [34, 35]. The first coronary artery bypass in KD was also reported at this time [36].

2011-2015

The first, and so far the only, epidemiologic study on KD from India was published in 2011 [7]. This suggested that the incidence of KD at Chandigarh is at least 4.54 / 100,000 children below 15 years of age [7]. This figure is probably an underestimate as many children with KD are still being missed and there is no way to ascertain how many children are being missed.

Over the years, KD has emerged as an important pediatric diagnosis and pediatricians in India are now familiar with the finer nuances of this disease. 'Incomplete' and 'atypical' forms of KD are now being increasingly diagnosed and reported [37,38]. Difficult patients with KD, as for instance those with paucity of clinical signs, are also being reported [40]. And this is a reflection of the growing confidence amongst pediatricians in India in recognizing and managing the wide clinical spectrum of this common pediatric vasculitis. More importantly, the scepticism associated with the diagnosis of KD is now no longer discernible. Long term follow-up studies on children with KD are making their appearance. Some reports on late coronary sequelae of KD in childhood have also emerged. Kohli, *et al*. [40] reported percutaneous transluminal coronary angioplasty in a young child with KD .

KD AS A CLINICAL DIAGNOSIS – WHAT EVERY PEDIATRICIAN SHOULD KNOW

1. Epidemiological trends suggest that incidence of KD is continuing to increase in several Asian countries (*e.g.* Japan, Korea, Taiwan). It is possible that the same may be applicable for India as well.

2. Although KD is commonly being diagnosed in many parts of the country, there are several regions (*e.g.* the North East) and states (*e.g.* Uttar Pradesh, Uttarakhand, Madhya Pradesh, Chhatisgarh, Bihar, Jharkhand, Haryana, Jammu and Kashmir) where the condition is not being diagnosed as frequently as it should be. We need information and education campaigns for both the health care professionals and the lay public to increase the awareness about this condition.

3. KD should no longer be considered an esoteric disorder to be diagnosed only when there is no other explanation for persisting fever in a young child. Rather this condition should be considered proactively in all children (especially infants) with fever beyond 5 days, so that diagnosis does not get delayed and treatment with intravenous immunoglobulin can be started before 10-12 days of fever.

4. When dealing with a febrile child, it is common in clinical practice to change antimicrobials or to prescribe 'higher antimicrobials' if fever persists beyond few days, even when there appears to be no discernible infective focus. One needs to refrain from (mis)using antimicrobials empirically in this manner. Rather one should deliberate and assess if fever is because of reasons other than a bacterial infection. It is often surprising how commonly KD can be lurking in the background under these circumstances.

5. The diagnostic criteria are mere guidelines and the extended spectrum of clinical presentation of KD goes far beyond these criteria.

6. Amongst infants and young children a significant proportion would not fulfil the diagnostic criteria as many would have 'incomplete' and 'atypical' forms of

KD. It is important to recognize that 'incomplete' and 'atypical' KD is, by no means, mild KD. On the contrary, these children often have devastating coronary sequelae as the diagnosis and treatment often gets delayed [1-3].

7. Anecdotal experience suggests that there are significant delays in diagnosis of KD in India, especially in areas and regions where this condition is still not being diagnosed frequently [42].

8. KD has a much higher mortality in India than in developed countries. In the Chandigarh cohort, the mortality rate over the last 20 years is 0.8%, as compared to 0.01-0.08% in children in developed countries [43]. This has to change.

9. It cannot be overemphasized that the prime responsibility for diagnosing KD, is that of the pediatrician (or physician) and not the cardiologist (or pediatric cardiologist). In the vast majority of cases, an echocardiography is not necessary for the initial diagnosis of KD. While it is desirable to have a pediatric cardiologist for assessment of coronary arteries in young children, the primary diagnosis of KD in the vast majority of cases remains clinical and one need not delay administration of immunoglobulin just because an echocardiography examination has not been performed.

10. Coronary artery abnormalities are often not discernible on echocardiography in the first week of illness [1-3]. A 'normal' echocardiogram in the first few days of the illness should, therefore, not lead to complacency. Ideally, echocardiography should be repeated several times during the initial hospitalization and subsequently on follow-up. Coronary artery 'z' scores must be recorded at each examination [43].

PUBLIC HEALTH IMPORTANCE OF KD FOR INDIA

From an esoteric disorder that was first described 48 years ago, we are now at the threshold of KD being considered a disease of public health importance. KD, and not rheumatic fever, may soon turn out to be the commonest cause of acquired heart disease amongst children in India just as in developed countries. At Chandigarh, we are now diagnosing KD at least ten times more commonly than rheumatic fever [5].

Prospectively collated data from several Asian countries have suggested that incidence of KD has continued to increase over the last 20 years [4-6]. Unfortunately, similar nationwide data are not available from India at present (7). Based on anecdotal experience, however, it is obvious that KD ascertainment over the last twp decades has increased significantly in several cities across the country [5]. However, it is also true that the diagnosis of KD is still not being made frequently in small towns and villages of our country. Large swathes of population are, therefore, potentially at risk of misdiagnosis or underdiagnosis. As a result it is reasonable to assume that majority of children with KD in India are, at present, not being diagnosed and treated.

Given that almost a fourth of children with untreated KD develop coronary artery abnormalities [1-3], it is obvious that many would go on to develop coronary sequelae in young adulthood. Giant aneurysms in KD almost never revert to normal [1-3]. Even when coronary arteries regain their normal anatomical architecture, recent imaging studies suggest that there are significant functional defects in these arteries [45]. Coronary artery abnormalities also predispose to premature atherosclerosis.

This potential cardiac burden, largely unrecognized by health administrators and health care planners at present, needs to be taken into account while apportioning scarce health care resources in a country like India. Unfortunately, these coronary artery sequelae develop at a time when these individuals are at the peak of their economic productivity. As pediatricians, we must realize that a large component of this cardiac burden is preventable by early diagnosis and treatment. Like acute rheumatic fever, KD presents a unique opportunity to pediatricians to intervene and use their diagnostic skills in preventive care.

Cardiologists must note that adult coronary artery disease secondary to undiagnosed and untreated KD in childhood is now a reality [46]. Amongst young adults with unexpected coronary events, especially those with no adverse risk factors or family history of coronary disease, the possibility of an underlying KD can never be discounted. Coronary angiography performed at this time may also not be able to resolve this dilemma as differentiation between atherosclerotic coronary artery disease and that due to KD sequelae may not always be easy. Coronary aneurysms seen during the early phase of KD usually heal and regress in size and often develop stenoses that may look morphologically similar to atherosclerotic changes on angiography. The coronary arteries in KD, however, have a much higher calcium score than that seen in atherosclerosis [47].

EPILOGUE

In conclusion, there is no doubt that over the last 20 years pediatricians in India have made remarkable progress in

ascertainment of KD. India is one of the very few countries to be hosting single-theme KD Summits, albeit biennially at present. That this enigmatic condition has generated intense academic interest in our country is obvious from the number of publications on the subject which have shown a quantum leap over the last few years. And what is most gratifying is the fact that these have emanated from different parts of the country. However, it is a sobering thought that many (in fact most) children with KD are still not being diagnosed or offered immunoglobulin therapy. A lot more needs to be done as far as increasing awareness about this condition is concerned. KD remains a challenge for all pediatricians in the country.

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