

## **Impressions of Kawasaki Syndrome in India**

Kawasaki Syndrome (KS) is the most common cause of acquired heart disease in the U.S. and Japan. Despite more than 40 years of research, its cause remains a mystery. Untreated children with KS are at risk for development of potentially fatal coronary artery aneurysms. Based on our research, there have been two distinctive patterns for the emergence of KS. In Europe and the U.S., KS existed in the pediatric population for more than a century but was hidden under the rubric of different diseases such as scarlet fever, Stevens Johnson syndrome, and rheumatic fever(1). When KS finally was recognized as a distinct entity, the incidence was low, between 15-20 per 100,000 children less than 5 years of age. In contrast, in Japan, we speculate that in the 1950s exposure to the KS agent(s) in a highly susceptible, naive population resulted in nationwide epidemics followed by a relatively high endemic rate of 150 per 100,000 in children less than 5 years(2). Because cases of KS have been increasingly reported from India in the last several years(3-6), we wanted to investigate the emergence of this illness on the Indian subcontinent and compare and contrast it with the emergence of KS in other countries.

Our impressions reported here were based on physical examination of suspected and confirmed KS patients, interviews with 47 parents of children diagnosed with KS, and 52 experienced, senior pediatricians, trainees, cardiologists, and other subspecialists in four different geographic locations in India (Chandigarh, New Delhi, Trivandrum and Mumbai/Thane) over a 2-week period in

February 2006. These were supplemented by teleconferencing with pediatricians in three other regions (Bangalore, Kolkata, and Hyderabad). We also reviewed the English-language literature on KS in India beginning in 1977 with the first reported case(7).

From interviews with parents and physicians, review of the portable clinical record given to each family, and examination of KS patients, we discovered possible differences in the clinical presentation of KS in India as compared to other countries. First, while 85% of KS patients in the U.S. and Japan are less than 5 years of age, in India there was a higher proportion of older patients. Second, peeling of the extremities coincided with the acute phase of fever and often occurred within the first 10 days after fever onset. In the U.S. and Japan, this desquamation generally occurs after 10 days, during convalescence from KS. Third, thrombocytosis was frequently noted during the early, acute phase of the illness whereas in the U.S., only 50% of children presenting within the first 10 days after fever onset had a platelet count greater than 450,000/ $\mu$ L(8). Early peeling of the extremities and elevated platelet count were frequently cited as helpful in establishing the diagnosis of KS. Despite these apparent differences in clinical presentation and course of the illness which should be explored more fully, these cases seem to fit into the recognized spectrum of KS seen throughout the world.

We addressed the question of whether the increased diagnosis of KS in India represents the emerging recognition of an illness that has been obscured by misclassification as other pediatric disorders, or whether KS is actually new to India. In our interviews, we asked

physicians questions about where and when they saw their first patient who, in retrospect, fulfilled the criteria for KS. We also asked under which categories might patients with KS be misclassified and if the current increase in numbers of KS patients in India is related to increased case ascertainment or an actual increase in KS incidence. There was general consensus among the physicians that the number of diagnosed cases of KS is increasing in India. At first, many physicians responded that increased awareness of the syndrome accounted for the growing incidence and that KS most likely had been misclassified as drug reactions or viral or bacterial toxin-mediated illness. However, on further reflection, the majority of interviewees thought it unlikely that KS cases had been missed in large numbers previously and that the recent increase in KS diagnoses reflected an actual increased incidence(9).

In our studies of the history of KS in different countries, we have described two different patterns for the emergence of KS. A fatal case diagnosed as “scarlatinal dropsy” associated with thrombosed coronary artery aneurysms resembling KS was documented in Britain as early as 1871(10). Since that time there is a clear record of the clinical course and autopsies of infants and children who died with a systemic vasculitis and coronary artery aneurysms with thrombosis that meet the current KS criteria(1). Such cases were reported in the literature with increasing frequency in the Americas and Europe starting in the 1930s(1,2). These reports emphasized damage to the coronary arteries out of proportion to systemic arteries and the cause of death was invariably thrombosis with myocardial infarction. By 1963, the numbers of cases had grown sufficiently in the U.S. that the pathologists Roberts and Fetterman brought them together under the rubric of

Infantile Periarteritis Nodosa (IPN)(11). In the early 1970s, fatal cases of KS were described from Hawaii and Japan and in 1977 Landing and Larson concluded that IPN and KS are part of a spectrum of the same illness(12). Cases of milder, self-limited illness that in retrospect fulfilled the clinical criteria for KS were reported in the U.S. starting in the late 1940s and were classified as Stevens Johnson syndrome(1,2).

In contrast, KS appears to have emerged in Japan beginning in the 1950s. No cases, either fatal or non-fatal, were uncovered prior to 1947 despite extensive searches for such cases through review of hospital records and interviews with senior pediatricians(13,1). Unlike in the West, there were no reports of fatal cases of IPN from Japan prior to the early 1960s. Following the report by Kawasaki in 1967, there was a precipitous rise in non-fatal cases accompanied by three major nation-wide epidemics in 1978, 1982, and 1986, which suggested the introduction of a new agent into a highly susceptible population(14). Numbers of cases continued to rise until plateauing in recent years at approximately 8,000 new cases of KS/year (150/100,000 children <5 yrs of age).

Understanding the trajectory of KS incidence in India depends on whether KS is new or old in India and may have profound implications for estimating the number of children at risk of developing potentially fatal coronary artery damage. If KS is new to India and the incidence is increasing and has not yet plateaued, KS in India may follow a pattern similar to that of Japan. There are an estimated 120 million children less than 5 years of age in India(15). If the rising KS incidence reaches levels similar to Japan, this would result in 180,000 new KS cases annually. If KS is not new to India and the incidence rises to a level similar to that in the U.S., there will

be an estimated 18,000 new cases per year. However, these estimates must be adapted for the genetic susceptibility and other demographic features that may influence the incidence of KS in India. Whether KS is new or old in India, the KS disease burden is likely to pose a significant challenge to the health care system in India in the coming years due to the high cost of treatment and the potential for lifelong cardiovascular sequelae.

The impressions reported here need to be tested by standard research methods. The incidence of KS can best be addressed by collaborative efforts to establish KS registries across India to determine the burden of KS in different regions and among different genetic and cultural groups. Efforts should continue to increase physician awareness and to encourage research on the characterization of KS in India with emphasis on possible differences in clinical presentation, disease course, and outcome in Indian children. One impediment to the evaluation and treatment of cardiovascular sequelae in these children is the scarcity of pediatric cardiologists to perform echocardiographic imaging of the coronary arteries. Work to develop criteria for normal coronary artery internal diameters in southern Indian children should be validated and adapted for different populations throughout India(16). Educational efforts by parent groups in Chandigarh and New Delhi to increase lay person awareness of KS serve as a model that should be emulated in other parts of the country. Similarly, the physician "ready reckoner" developed from the Mumbai KS Study group provides easily accessible information for physicians regarding KS diagnosis and treatment(5). Making such a pamphlet readily available throughout India will increase physician awareness of KS. Finally, investigating the emergence of KS in India and its distinct clinical manifestations

in Indian children will make important contributions to understanding this mysterious illness in children throughout the world.

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archive by permission through the KD History website: [http://www.emory.edu/CHCS/p\\_histmed\\_Kawasaki.htm](http://www.emory.edu/CHCS/p_histmed_Kawasaki.htm)

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