

Fifty Years of Kawasaki Disease – A Tribute to Dr Tomisaku Kawasaki

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It has been 50 years since the legendary Japanese pediatrician, Dr Tomisaku Kawasaki, published his classic paper in 1967. Little was he to know at that time that this condition would not only be known after his name but would also become the commonest cause of acquired heart disease in children in most of the developed world. The etiology of this condition continues to remain an enigma, and the diagnosis is still based on a set of criteria that are entirely clinical. All pediatricians must be familiar with the various clinical presentations of this disease because delays in diagnosis and treatment can have disastrous consequences.

Keywords: *Diagnosis, History, Kawasaki disease, Treatment.*

The year 2017 marks the 50th anniversary of the landmark publication in 1967 by the Japanese paediatrician, Dr Tomisaku Kawasaki, who is arguably one of the greatest living medical legends today [1,2]. At that time Dr Kawasaki was working at the Japanese Red Cross Hospital in Tokyo, and was not holding any academic position. His original manuscript was entitled, “Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children”, and was published in the Japanese Journal of Allergy [1]. The manuscript detailed the clinical features of 50 children with this ‘new’ disease entity that he had seen between 1961 and 1967. Dr Kawasaki’s original report is testimony to his astute clinical judgment and meticulous record keeping. He showed that this condition was quite different from ‘atypical scarlet fever’ that many of his peers in the Japanese academia thought it to be [3]. Likewise, this condition was quite unlike Stevens Johnson Syndrome (SJS) that was also proffered as a clinical possibility by some of his colleagues [3]. What is most noteworthy is that he continued to maintain his stand that what he had documented was indeed a disease entity not hitherto described, and held on to his belief amidst stiff and growing opposition from several academics in Japan who refused to accept that this was a new discovery [3]. This opposition continued for several years. Dr Kawasaki’s manuscript ran over 44 pages, and it meticulously described the salient clinical features of these patients and elaborated on the differences between this entity *vis-a-vis* scarlet fever and SJS [4]. Little was Dr. Kawasaki, however, to realize at that time that this seemingly innocuous and self-limiting condition that he

had seen would one day be recognized as the leading cause of acquired heart disease in children [5,6].

Epidemiologic data suggest that Kawasaki disease (KD) is now the commonest cause of acquired heart disease amongst children in several Asian countries (*e.g.*, Japan, Korea and Taiwan), Europe and North America [7,8]. Japan reports the world’s highest incidence of KD at 265/100,00 children below the age of five years [7] while the corresponding figures from Korea and Taiwan are 194 and 69.5, respectively [9,10]. Approximately 1% of children born in Japan develop KD by the age of 10 [7]. With a population of 127 million, Japan reports upwards of 13,000 children with KD every year [7]. What is of even more concern is the fact the incidence of KD continues to rise in countries such as Japan, Korea and Taiwan [7-10]. On the other hand, the incidence of KD in Europe and North America (5-30/100,000 children below the age of five years) and seems to have plateaued [8]. Epidemiologic data and anecdotal reports from several cities and regions in China and India seem to point that children with KD are now being increasingly recognized in these two countries that are home to one-third of the world’s population [11-17]. Whether this increased reporting from China and India is due to greater ascertainment or a true increase in incidence is a matter of conjecture as nationwide data are presently not available from either of the two countries [8,16-19]. Concomitant with a perceived gradual decrease in incidence of rheumatic fever [20], it is likely that KD may soon replace rheumatic fever as the commonest cause of acquired heart disease in children in these countries just as in the developed world [21].

Like many other vasculitides, the diagnosis of KD rests on clinical findings alone, and there is no pathognomonic laboratory test to help the clinician in confirming the diagnosis [22]. The diagnostic criteria have evolved over a period of time but even the most recent version proffered by the American Heart Association (AHA) is not significantly different from the original criteria proposed by Dr. Kawasaki in 1967 [22-24]. The criteria can help the clinician in arriving at a diagnosis, but the sensitivity and specificity of these criteria is not known [22]. To further complicate matters, some children appear to develop 'incomplete' or 'atypical' forms of the disease [22]. These children would not fulfil the diagnostic criteria but nevertheless have the predisposition to develop the same cardiac sequelae as other children with complete KD. There is some evidence that children with incomplete KD may, in fact, develop more coronary complications as treatment often gets delayed because of delays in diagnosis [25]. If one were to diagnose KD based strictly on the requisite number of criteria being fulfilled, the specificity of the diagnosis would be very high but this would be at the cost of sensitivity. It cannot be overemphasized that the clinical consequences of a missed diagnosis of KD can be catastrophic [26]. In infants with KD, and especially in babies below 6 months, it is not unusual to have patients who do not fulfil the aforesaid criteria even though they have a much greater chance of developing coronary artery abnormalities [27,28]. One has no choice, therefore, but to use one's clinical judgement whenever a therapeutic decision has to be made while managing young children with probable KD [27]. For the paediatrician, it is always a very challenging exercise to avoid the pitfalls of both under and over-diagnosis of this condition. While under-diagnosis can result in devastating coronary and non-coronary cardiac sequelae, over-diagnosis would result in administration of an expensive therapeutic agent, *viz.* Intravenous immunoglobulin (IVIg) [29].

The standard of care for children with KD is administration of a single dose of IVIg (2 g/kg) along with aspirin [22]. Approximately 10-15% of patients may, however, continue to remain febrile or may have recrudescence of fever after the first dose of IVIg [22]. Such patients are said to have IVIg resistance and require additional forms of therapy. These include administration of a repeat dose of IVIg, glucocorticoids (pulse methylprednisolone followed by tapering doses of prednisolone), or biological agents such as anti-tumor necrosis factor- α (anti-TNF α) agents (*i.e.* infliximab) [30,31], or interleukin-1 (IL-1) receptor antagonists (*i.e.* anakinra) [32].

KD is a common childhood condition that can have significant long-term sequelae in the form of coronary artery abnormalities and myocarditis if the diagnosis is not made promptly and appropriate treatment initiated [22]. All pediatricians should be aware of this condition and the varying clinical manifestations of the disorder [29]. Children with undiagnosed and untreated KD are known to present in young adulthood with several serious cardiac events such as myocardial infarction, congestive cardiac failure, arrhythmias and even sudden death [26,33,34]. Most of these consequences are eminently preventable. It is, therefore, imperative upon pediatricians to recognize the expanded spectrum of KD, make the diagnosis expeditiously, and initiate appropriate treatment promptly.

We pediatricians owe a debt of gratitude to the gentle master, Dr Tomisaku Kawasaki, for his painstaking efforts in recording seemingly banal clinical findings that were to constitute the principal criteria for diagnosis of a new clinical condition, and which was to ultimately bear his name. The etiology of KD continues to remain an enigma even 50 years after its original identification and the diagnosis can test the acumen of even the most skilled and experienced pediatrician [35]. The use of micro-array technology for arriving at a diagnosis of KD, and differentiating it from other febrile illnesses of children, is likely to become a reality in the near future, and one can expect exciting developments in this challenging field. Fortunately, the treatment of this disorder is relatively straightforward and easily available.

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