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REVIEW
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A Tale of a Trail on How It Takes 5 Days of Kawasaki Disease to Initiate Coronary Artery Injury and Change the Lives of Children

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ABSTRACT

Many articles written on Kawasaki disease explain the disease and the history of an acute inflammatory dysregulation that typically affects preschool children and does not spare older ones. Six decades have passed since the discovery of the disease in Japan, yet there are parts of the world where the disease passes unacknowledged, diagnosis is delayed, or basic treatments are not readily available. The burden of Kawasaki disease is on every health-care provider who attends to children's health. It takes 5 days for the disease to initiate coronary artery injury in a child's heart, compared to 5 decades of lifetime atherosclerosis. Challenges facing patients, families, and physicians may not be overcome unless we advocate for the disease recognition and seek support for affordable, timely treatment, impactful research, and dissemination of knowledge. The purpose of this review is to provide a comprehensive review of the history of Kawasaki disease and how it has affected children's health worldwide over the last 6 decades. The review also raises current challenges facing the fight against Kawasaki disease. In an effort to bring Kawasaki disease advocates together in a landing zone, an internet hub for Kawasaki disease experts and enthusiasts has been created: the International Kawasaki Disease Society (presently a concept idea) and a dedicated website, www.ikds-org.

Keywords: Kawasaki disease, advocacy, coronary artery

INTRODUCTION

In the year 2024 (August 26-29), the 14th International Kawasaki Disease Symposium (IKDS-2024) will be held in Montreal, Quebec, Canada. This cornerstone conference has a long history of bringing together Kawasaki disease (KD) experts from the medical community worldwide, where every 3 years clinicians and researchers share their experience and discoveries. The tradition started in 1984 and has continued ever since, with the leadership of the late sensei Dr. Tomisaku Kawasaki (1925-2020). As a pediatrician working at the Tokyo Red Cross hospital, Dr. Kawasaki noticed from the early 1960s a constellation of symptoms occurring in several Japanese children, some of whom eventually succumbed as a consequence of thrombosed or ruptured coronary artery aneurysms. Following the first publication of his series in 1967, this new clinical manifestation was dubbed "mucocutaneous lymph node syndrome," a name derived from the title of the article.[1] The condition resembled a variety of infectious and inflammatory childhood conditions, yet it caused necrotizing arteritis and had a particular tropism to the heart and the coronary arteries. Years passed and the new name of the new medical condition alternated between Kawasaki's syndrome and Kawasaki's disease. Kawasaki's disease had no clear etiology, displayed no evidence of particular inheritance, and, unlike most febrile illnesses affecting young children, KD was not (and still is not) contagious. Although KD remains noncontagious, an infectious agent (or agents) triggers the condition in genetically predisposed individuals.[2] Beyond the genetic predisposition to develop KD, another reproducible observation across nations and ethnicities is the fact that boys are more affected by the disease at a 1.5 : 1 male-to-female ratio, and boys are more prone to develop complications, such as coronary artery aneurysms.[3]

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Nowadays, the incidence rates in the United States varies between 20 and 25 per 100000 children <5 years of age; the incidence is 10 times higher in Japan. Future trend predictions estimates suggest that 1 in 1600 Americans will have a history of childhood KD by 2030.[4]

Fast forward 53 years, a constellation of symptoms—reminiscent of the symptoms that compose the clinical criteria of KD[5]—started to develop in young children exposed to or infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus.[6,7] This new entity had a handful of diagnostic criteria depending on the various health authorities issuing the recommendations, with the multisystem inflammatory syndrome of childhood (MIS-C) criteria by the US Centers for Disease Control and Prevention becoming the most widely used.[8] The uncertainty about the pathophysiology and the treatment of MIS-C loomed initially despite the certainty that SARS-CoV2 was the triggering factor. Nevertheless, MIS-C (rightfully recognized as a syndrome), was rather rapidly put in check thanks to 5 decades of experience with and research on KD. The rightful focus on this new syndrome, however, caused a shift of awareness from KD as suggested by an early call for awareness[9] and by subsequent missed severe cases of KD amid the pandemic.[10] Finally, MIS-C turned out to cause more cardiovascular shock and transitory myocardial dysfunction whereas KD continued to injure primarily the coronary arteries in a higher proportion and in a much more severe fashion.[11]

There are multiple ways to answer what KD is, if asked. The narrative goes from explaining the clinical presentation, to the complete or incomplete criteria, to unknown etiology but good efficient therapy, then to resistance to standard treatment and supplemental regimens, and down to coronary complications. The classical clinical criteria remain important to acknowledge in addition to 5 days of fever or more (erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash: maculopapular, diffuse erythroderma, or erythema multiforme-like; erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; cervical lymphadenopathy). However, the importance of fulfilling the diagnostic criteria to diagnose KD has been challenged in 2004 since children with incomplete criteria run at least the same risk level for coronary artery complications.[12] Timely diagnosis and treatment remain of prime importance to reduce the coronary aneurysm complication rate from the historic figure of 25%-30% to under 5%. Hence, the fact of the matter is the importance of what KD does instead of what it is. Here is what I found most efficient to capture the attention and explain why it is important to understand KD. In essence, it takes 5 days for KD to initiate coronary artery injury on a child's heart compared to 5 decades of lifetime atherosclerosis. The superacute inflammatory dysregulation in KD will trigger a torrential, devastating necrotizing arteritis on the coronary arteries, followed by neointima remodeling, luminal myofibroblastic proliferation, in situ chronic inflammation, calcium deposits, and macrophage infiltrates.[13] Subsequent coronary artery stenoses and thromboses (let alone the now rare aneurysmal rupture) make KD the primary cause of childhood myocardial infarction and the inherent morbidity and mortality. KD is also the first acquired heart disease altogether in economically advanced nations, and the second cause of acquired heart disease in rheumatic heart disease endemic regions.[14]

Kawasaki disease is classified among the rare and orphan diseases. Nevertheless, is KD truly that rare? All reports have repeatedly demonstrated how "common" KD is in several parts of the globe.[15] High and increasing incidence rates are primarily attributed to improved awareness, which increases diagnostic propensity. In the US alone, acute KD admissions to the hospital represent 0.85 for every thousand hospitalizations.[16] To put into perspective, the incidence of congenital heart defects is 2 per 1000 live births in the same country.[17] Another wave of recorded incremental incidence of KD followed the 2004 guidelines focusing on diagnosis despite the situation where coinfection may be present (therefore KD is no longer a diagnosis of exclusion) and recognizing cases even if the complete clinical criteria are not met (known as incomplete KD).[18] Patients with incomplete KD (formerly referred to as atypical KD) are at similar or higher risk for coronary artery complications compared to complete or typical cases.[19] National societies for KD, such as the Japanese Society of Kawasaki Disease,[20] an obvious leader from that perspective, and the Japan Kawasaki Disease Research Center (a nonprofit organization founded by the late Dr. Tomisaku Kawasaki) are naturally and inherently present in Eastern Asian countries, countries with the highest incidence rates for the disease, predominantly due to genetic predisposition.[21] Nevertheless, a third wave of enhanced diagnostic efforts (and subsequently timely administration of effective therapy) is coming along by engaging parent–patient advocacy groups on regional or national levels (a handful of foundations are active and available in different countries). Similarly, regional, national, multinational, or multi-institutional collaborations are empowering better understanding of the disease and fostering widespread and advanced knowledge and expertise in KD among the group members but also thanks to the synaptic links of these professional-based collaborative groups.[22-28]

Networking is essential to the success of any organization. Kawasaki disease, however, is not housed by an international organization despite various national groups. Kawasaki disease experts are not solely committed to KD, as health-care professionals, and scientific researchers cannot afford to commit exclusively to this disease alone. There are alarmingly insufficient funds committed to solving the problems of KD. Apart from the Japan KD research center, a program (partially) supported by the Japan Ministry of Health, KD researchers in general suffer from the scarcity of dedicated funds, including but not limited to competitive-based resources. In addition, the pharmaceutical industry is bound by legal, ethical, and heavy regulations that restrain those companies from providing the needed support to KD research and KD-centered scientific conferences. While intravenous immunoglobulin is the only formally approved therapy to treat KD, therapy must be initiated within the efficacy therapeutic window (before 10 days from the onset of fever), hence the importance of timely diagnosis. Nearly 20% of patients do not respond to immunoglobulin infusion (2 g/kg over 10-12 hours) and would require adjuvant or rescue therapy with molecules that are not officially approved for KD (corticosteroids, immunosuppressing agents, biological inflammatory modulators). Other molecules used on a daily basis include antiplatelet and anticoagulant drugs, to

prevent intracoronary platelet aggregation and clotting. For off-label use of medications, the prescribing physician carries the responsibility simply because KD does not represent a large market for drug companies to conduct the required clinical trials and seek (the expensive process of) label approval by the different health authorities.

Unfortunately, this is not the only concern that KD patients (and parents) face. Kawasaki disease kids (80% of them diagnosed during their preschool age, and nearly all of them before adulthood) do grow up to reach adulthood, with many of them beyond middle age already. Yet the transition from pediatric medical management to adult specialists' care is yet to be formally established.[29] In Japan, for instance, more than 40% of patients with KD carrying coronary artery lesions had been lost to follow-up according to a 2018 survey.[30] Perhaps adult congenital cardiology specialists should take on the task, easier said than done. It has taken several decades for adult cardiologists to structure educational programs and formal training curricula and expertise in adult congenital heart disease. Specialized clinics, savant societies, and focused scientific conferences and dedicated sessions are a reality now for this discipline. This is not true for adult patients with KD sequelae; however, coronary sequela, for that matter, not to underestimate other needs for those patients, is not the same as atherosclerosis disease either. The IKDS-2024 program agenda addresses this very topic in a dedicated mini-summit as part of the core curriculum of the meeting.

PERSPECTIVES AND OPPORTUNITIES FOR INTERNATIONAL COLLABORATION

In an effort to bring KD advocates together, we have recently created a landing zone, an Internet hub for KD experts and enthusiasts, the International Kawasaki Disease Society (presently a concept idea), and a dedicated website (www.ikds-org). Talks are underway with former presidents of the previous international KD symposia and several key players and group leaders worldwide to bring the idea of an international KD society to implementation. We expect that the 14th International Kawasaki Disease Symposium, the IKDS-2024, with the theme of "Fostering global collaborations to solve KD" will factually set the cornerstone of this international umbrella bridging existing and emerging collaborative KD groups under 1 communicative platform in propulsive dynamics toward the future of the disease knowledge and the solving of the many mysteries that lie underneath. The IKDS-2024 will be more than a scientific symposium; it will be a summit where decisions of future directions will be discussed, a scholastic teaching experience with hands-on learning sessions, and a savant society confederating existing and future collaborative efforts for KD.

CONCLUSION

The burden of KD is on every health-care provider who attends to children's health. It takes 5 days for the disease to initiate coronary artery injury in a child's heart compared to 5 decades of lifetime atherosclerosis. Timely diagnosis and therapy remain the cornerstone to curtail the complication rate of KD and to secure the resolution of the inflammatory processes involved. The prognosis of KD relies not only on therapy but on large-scale awareness and advocacy.

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