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Review Article

Kawasaki Disease as the Immune-Mediated Echo of a Viral Infection

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Abstract. Although the etiology of Kawasaki disease (KD) remains elusive, the available evidence indicates that the primum movens may be a dysregulated immune response to various microbial agents, leading to cytokine cascade and endothelial cell activation in patients with KD. Documented infections by different viruses in many individual cases have been largely reported and are discussed herein, but attempts to demonstrate their causative role in the distinctive KD scenario and KD epidemiological features have been disappointing. To date, no definite link has been irrefutably found between a single infection and KD.

Keywords: Kawasaki disease; Viral infection; Virus; Child; Personalized medicine.

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The History of Kawasaki Disease. Almost 60 years ago, dr. Tomisaku Kawasaki noted, for the first time, a strange association of symptoms in a 4-year-old boy who was hospitalized at the Chiba University. The child had prolonged high fever, conjunctivitis, a widespread rash all over the body, and a bright-red tongue. However, he could not explain that disease, thinking to an allergy or any infectious diseases. Antibiotics were ineffective in treating that boy's symptoms, which subsided only after two weeks, also revealing specific desquamation of the fingers and toes. One year later, another child was hospitalized with those same symptoms, and dr. Kawasaki convinced himself that a mysterious illness could affect children. In 1967 he published a 44-page report of all hospitalized patients having that illness (that he named "acute febrile mucocutaneous lymph node syndrome") in the Japanese journal "Arerugi", usually dedicated to allergology, which was based on a diligent 6-year observation of 50 patients.[1] The eponym of Kawasaki disease (KD) was coined later, when an international journal offered a large amount of space to the description of this illness.[2] With some cases of sudden death occurring after an apparent resolution of KD, the issue started to gain more and more attention by the scientific community, and pediatric textbooks started to report on this condition.

A Systemic Vasculitis is the Key to Explain Kawasaki Disease. In plain terms, KD is a systemic vasculitis that mainly and typically occurs in infants and children less than five years: the most ominous complication of patients with KD is the occurrence of coronary artery abnormalities (CAA).[3] For this reason, KD is actually the leading cause of acquired pediatric heart disease in the developed world.[4] Many reports found that coronary arteritis occurred at the highest incidence, but that vasculitis developed at various sites throughout the body. Vascular lesions of KD may start in the tunica interna and externa of medium-sized muscular arteries, such as the coronary arteries, but also in arterioles, venules and

capillaries, while inflammation disseminates to large arteries including the coronary arteries.[5,6] The media of affected vessels demonstrates edematous dissociation of the smooth muscle cells, while endothelial cell swelling and subendothelial edema are seen. An influx of neutrophils can be observed in the early stages of KD, with a rapid transition to large mononuclear cells in concert with lymphocytes and IgA plasma cells. Destruction of the internal elastic lamina and an eventual fibroblast proliferation can occur later. This active inflammation is replaced over several weeks to months by progressive fibrosis, with scar formation and remodeling.[7]

The Clinical Chameleon of Kawasaki Disease. The classic diagnosis of KD has been historically based on the presence of 5 days of fever and a typical constellation of nonspecific clinical signs described in 1967 by dr. Kawasaki: upholding the diagnosis of KD requires that highly swinging fever is combined with at least 4 out of 5 "main" clinical features: [a] bilateral non-exudative conjunctivitis, [b] unilateral cervical lymphadenopathy, [c] polymorphous rash, [d] changes in the extremities (mainly in the form of angioedema) or in the perineal region (an early-onset desquamating rash) and [e] changes in the lips and/or oral cavity (dry fissured or reddened lips with a strawberry-like tongue).[8] Although the clinical clues of KD are easily recognizable, its underlying mechanisms are under deep investigation and remain poorly understood. Treatment of KD requires intravenous immunoglobulin (IVIG) and aspirin during the first ten days of illness, and its ultimate goal is avoiding the occurrence of CAA.[9] Mostly in the case of resistance to IVIG, inflammatory cells reach the vasa vasorum of coronary arteries with the risk of fragmentation of the internal lamina and damage to the media, resulting in the formation of CAA.[10] Higher values of C-reactive protein and younger age at onset are crucial points in determining respectively a failure in response to IVIG and a higher risk that the disease could be complicated by CAA.[11] Early ascertainment of non-responders to IVIG who might require additional therapies reducing the development of CAA is still a challenge.[12] With improved treatment methods and different drugs useful for refractory cases, the mortality rate of KD has dropped dramatically in recent years. However, despite increased awareness, the number of patients with KD presenting with incomplete or atypical features is increasing across the world. Incomplete cases of KD are characterized by less than four main clinical signs and atypical ones by a broad range of unusual clinical features, including aseptic meningitis, peripheral facial nerve palsy, liver impairment with jaundice, gallbladder hydrops, pneumonia-like disease, and even macrophage activation syndrome.[13,14]

Different Potential Causes, One Resulting Disease. Despite extensive research, the etiology of KD is far to be unraveled, and no single pathognomonic clinical or laboratory finding for diagnosis has been identified. Indeed, the occurrence of KD in epidemics, as shown by nationwide epidemiologic surveys conducted with biennial frequency since 1970, reveals a potential relationship of KD with an infectious disease. A number of infectious agents, both bacterial and viral, have been isolated from patients with KD through the years,[15] but also non-infectious triggers are presumed to cause the disease.[16] Further KD characteristics such as high-grade fever, elevated acute-phase reactants, and elevated white blood cell count strongly suggest an infectious cause, and in particular, some characteristics may suggest a viral etiology, such as the self-limited course of KD, skin rash and conjunctivitis. A host of reports have clarified the distinct seasonality of KD in geographically distinct regions of the northern hemisphere, revealing that various triggers may be operating at different times of the year in various geospatial clustering of KD cases:[17] the seasonality of KD, with winter peaks in Japan and winter-spring predominance in the USA or in many other temperate areas, is highly suggestive of a viral etiology.[18] Shimizu et al. found a seasonal effect also on the response to IVIG treatment, with more patients manifesting resistance to IVIG in the warm seasons from May to October, but no differences in the general outcome of CAA.[19] Several epidemiological studies have also demonstrated that KD is frequently associated with a previous respiratory illness; however, no differences have been found in children stratified according to positive or negative respiratory viral testing; in fact, a positive test for respiratory viruses at the time of presentation should not be used to exclude the diagnosis of KD.[20]

A Viral Infection to Switch on Kawasaki Disease. Searching for papers dedicated to KD and published in the last 35 years through PubMed (matching the terms "KD" and "virus" or "viral infection"), a list of viral agents hypothetically associated with KD can be drawn (see **Table 1**). Viral respiratory infections have been commonly found at the diagnosis of KD,[21] but they do not seem to affect patients' response to IVIG or influence the overall outcome.[22] The oldest reports date back to 1983 when rotavirus was found in the feces of children with KD[23] and to 1985 when parainfluenza virus and adenovirus were encountered.[24,25] A molecular-based adenovirus detection is relatively frequent in KD patients but should be interpreted with caution.[26] Indeed, 24 out of 25 children with adenovirus disease mimicking features of KD had a higher viral burden compared to those with KD and incidental adenovirus detection.[27] Anecdotal reports had been associated KD to human herpesvirus-6,

Table 1. Viral agents associated with Kawasaki disease.

Viral agent	*References*	*Year*	*First authors*	*Modality of study*
Rotavirus	23	1983	Matsuno	Hemagglutination on feces
Parainfluenza virus	24	1985	Johnson	Culture on pharyngeal swab
Adenovirus	25	1985	Embil	Autoptic result
Adenovirus	26,27	2013, 2016	Jaggi, Song	RT-PCR
Herpesvirus 6	28,29	1989, 1992	Okano, Hagiwara	Serum antibodies
Parvovirus B19	30,45	1995, 2019	Holm, Maggio	Serum antibodies
Cytomegalovirus	31	2008	Usta Guc	Serum antibodies
Epstein-Barr virus	32	1994	Kanegane	RT-PCR
Epstein-Barr virus	33,44	1990, 2019	Kikuta, Maggio	Serum antibodies
Measles virus	34	2000	Kuijpers	Clinical assessment
Herpes virus	35	2002	Shingadia	RT-PCR
Varicella-zoster virus	36	2004	Lee	Clinical assessment
Influenza virus	37,38,46	2011, 2015, 2019	Joshi, Huang, Wang	RT-PCR
Coxsackie B3 virus	39	2012	Rigante	Serum antibodies
Bocavirus	40,41,42,54	2007, 2011, 2014, 2019	Catalano-Pons, Santos, Bajolle, L'Huillier	RT-PCR
Torque teno virus 7	42	2018	Thissen	RT-PCR
New Haven coronavirus	48	2005	Esper	RT-PCR
Coronavirus NL63	49	2006	Dominguez	RT-PCR
Coronavirus 229E	50	2014	Shirato	Serum antibodies
Coronavirus	47	2014	Chang	RT-PCR
New coronavirus SARS-CoV-2	51,52,53	2020	Jones, Rivera-Figueroa, Verdoni	RT-PCR

parvovirus B19 and cytomegalovirus.[28-31] However, the highest number of KD reports has been related to Epstein-Barr virus,[32,33] while KD cases with a concomitant infection caused by measles virus,[34] herpesvirus,[35] varicella-zoster virus,[36] influenza virus,[37,38] coxsackie virus,[39] and bocavirus are mostly isolated reports.[40] In particular for bocavirus, its nucleic acid was found in the nasopharyngeal, serum and stool samples from 5/16 (31.2%) patients with KD by reverse transcriptase-polymerase chain reaction (RT-PCR).[41] A prospective study by Bajolle et al. revealed that bocavirus was present in the serum of 3/32 (9%) and in the nasopharyngeal aspirate of 7/32 (21.8%) patients with KD, who probably had a previous bocavirus infection heralding KD.[42] Metagenomic sequencing and PCR detected torque teno virus 7 in only 2/11 (18%) patients with KD prospectively evaluated for one year,[43] while the most recent reports have highlighted the association of KD with Epstein-Barr virus,[44] parvovirus B19[45] and influenza virus.[46]

The Outbreak of the New Coronavirus and Kawasaki Disease. The latest outbreak of the new coronavirus (HCoV) infection (named SARS-CoV-2) and the resulting pandemic threat to health worldwide has required strict social containment measures since February 2020, but has also spread the suspicion that this peculiar infection might trigger KD. As a matter of fact, HCoV has been associated with many reports of KD in the past: for instance, in a prospective case-controlled study among Taiwanese children it was isolated in 7.1% of cases.[47] In 2005 Esper et al. identified a novel human HCoV, named "New Haven," in the respiratory secretions from 8/11 children with KD.[48] However, in Denver (Colorado, USA) the prevalence of HCoV-NL63 infection was not higher in KD patients compared with non-KD controls.[49] The contribution of HCoV-229E infection in the development of KD was also brought in question by Shirato et al., who used immunofluorescence testing to detect virus-neutralizing antibodies in 15 patients with KD before IVIG treatment.[50] The first case of KD associated with a concomitant SARS-CoV-2 infection was a 6-month infant hospitalized in Palo Alto (California, USA). However, the clinical significance of patient's positive testing remained unclear in the setting of KD.[51] Furthermore, a 5-year-old Afro-American boy was found to have KD-related signs in Jackson (Mississippi, USA) in combination with severe acute respiratory distress and shock syndrome, referred to SARS-CoV-2 infection detected via RT-PCR from his nasopharyngeal swab.[52] In April 2020, Verdoni et al. reported a 30-fold increased incidence of KD-like syndrome in children living in the Bergamo province of Italy, after the SARS-CoV-2 epidemic began in that same area, also showing

higher rates of heart involvement and general features of macrophage activation or shock syndrome. The evidence of contact with the virus was confirmed by the presence of antibodies against SARS-CoV-2 in 8 out of 10 reported patients.[53] This study had the limitation of being based on a small case series, but suggested in-depth genetic analysis to investigate the potential susceptibility to KD after a triggering effect of SARS-CoV-2.

More recently, in the New York State (USA) during the period March-May 2020, a SARS-CoV-2-related multisystem inflammatory syndrome has been found in 95 patients younger than 21 years of all ethnic backgrounds: such patients presented an inflammatory vasculopathy showing some similarities to KD and toxic shock syndrome, and in particular nearly half of children 0 to 5 years, but only 12% of the adolescents 13 to 20 years of age had a discharge diagnosis of KD or atypical KD.[54] This study had the limitation of a presumed underestimation, possibly due to mild cases that did not require hospitalization.

The Evidence about Viral Contributors to Kawasaki Disease. Ultimately, viruses may be confounding bystanders in many descriptions of KD. However, intracytoplasmic inclusion bodies sharing morphologic features among several different RNA viral families have been found in autoptic tissues of patients deceased for KD.[55] Rowley et al. speculated that the development of KD could follow ubiquitous RNA viruses causing an asymptomatic infection or a very mild disease in the vast majority of children, but specifically "KD" in a subset of genetically selected people.[56] In addition, a pilot study investigating KD pathogenesis revealed specific viral signatures in 4/7 patients with KD via high-throughput sequencing on blood specimens, although 2 were corresponding to their vaccinal history (oral poliovirus and measles/mumps/rubella vaccine) and 2 to bocavirus and rhinovirus, which could suggest a temporal association with the disease.[57] Different studies have also found that an imbalance in the gut microbiota might interfere with the normal function of innate and adaptive immunity, and that variable microbiota interactions with environmental factors, mainly infectious agents, might drive the development of KD in a genetically susceptible child.[58] However, to date, no definite link has been irrefutably found between any viral agents and KD.

Conclusive Remarks. More than half a century after its discovery, it is frustrating to admit that KD is believed to be triggered by an infection, but that its direct unequivocal cause is unclear. Besides, at the age of 95, dr. Kawasaki remains very active and continues to support families with KD children through different nonprofit organizations. New theories about KD hypothesize that the disorder might be conceived as an autoinflammatory condition,[59] in which inflammation explodes without any involvement of autoimmune pathways and any sound relationship with microbial agents.[60-62] Although KD causal factors are still elusive, the available evidence indicates that the primum movens may be a dysregulation of immune responses to various infectious agents, i.e., a kind of immune-mediated "echo" induced also by a viral infection. Even if several data might suggest that KD is an infection-related clinical syndrome, which can develop only in children with a predisposing genetic background, our knowledge on both the infectious agents involved and genetic characteristics of susceptible children remains poor. Understanding the molecular players responsible for dysregulation of the immune response in KD will foster the development of improved predictive tools and a more rational use of therapeutic agents to decrease the risk of CAA in all children with KD.

In Memoriam. On June 5, 2020 dr. Tomisaku Kawasaki passed away at the age of 95: the news had a profound impact on many clinicians who dedicated their professional lives studying Kawasaki disease. He was a true model to all pediatricians, not only with regard to his clinical acumen but especially concerning his vibrant humanity. This article is sincerely dedicated to the memory of Tomisaku Kawasaki.

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