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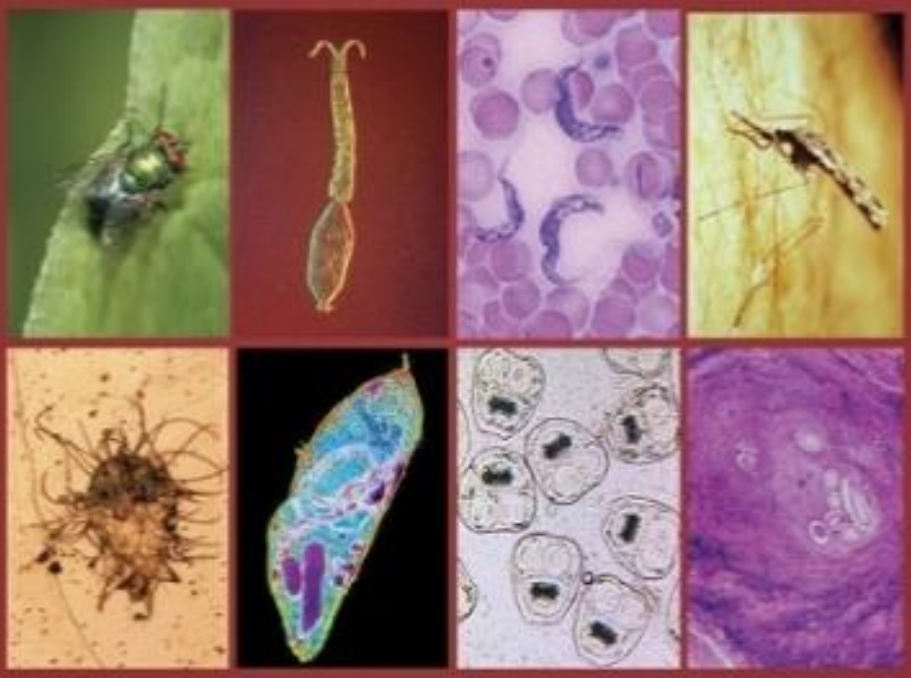

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Kawasaki Review: History, Etiology, Pathophysiology, Epidemiology and Treatment

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ABSTRACT

In 1961 the first case of Kawasaki disease which was an acute systemic vasculitis. Since then, the medical community has been continuously publishing papers to enhance our understanding of this disease. Asian countries such as Japan have higher prevalence rates of Kawasaki disease; in 2010, the yearly prevalence rate was 239 points per 100,000 children, and more recently it was 264 points per 100,000 children. The use of supporting laboratory tests and echocardiography is advised in order to identify patients who are susceptible but do not meet all diagnostic requirements. However, clinical findings are diagnostic for typical cases of Kawasaki disease. The most common complication is coronary aneurysm. An intravenous immunoglobulin as well as aspirin is used for Kawasaki disease treatment, however, if the cases do not improve a second dose of immunoglobulin is recommended. This review amid to present the basic knowledge and background about Kawasaki disease including etiology, diagnosis, epidemiology, treatment, management and control.

Overall, Kawasaki disease is still not completely understood, but with the right care and supervision, it is controllable. Prognosis can be greatly improved and associated problems can be decreased with prompt diagnosis and action. More studies and research need to focus on Kawasaki disease management and control.

INTRODUCTION

The Kawasaki disease enlarges, or inflames, the walls of the small to medium-sized blood vessels that supply blood to all parts of the body. Children with Kawasaki disease typically have heart artery disease. The heart receives oxygen-rich blood from those arteries. Kawasaki disease is also called mucocutaneous lymph node syndrome due to the fact that it also inflames the mucous membranes in the mouth, nose, eyes, and throat as well as glands known as lymph nodes (Ozen *et al.*, 2006).

Dr. Tomisaku Kawasaki first encountered Kawasaki disease (KD) in January 1961 when a male patient aged four years old exhibited symptoms including high fever, bilateral conjunctival hyperemia, reddish bleeding lips, strawberry tongue, and oral cavity erythema. That patient also showed cervical lymphadenopathy, erythema of the palms and soles, and generalized polymorphous erythema all over his body. Shortly after the previous symptoms, desquamation of the hands and feet occurred. Despite suggestions of scarlet fever and Stevens-Johnson syndrome, a definitive diagnosis was not made at discharge (Ozen *et al.*, 2006).

Dr. Kawasaki discovered a second case in 1962 that exhibited comparable features, and by October of the same year, he had discovered an additional 5 patients. He presented a paper including these seven cases at the "Chiba Prefecture Pediatric meeting", but at that time, no one gave him any positive feedback. Dr. Kawasaki saw 50 patients with similar symptoms over the next five years following the first case. He then published research titled "Acute febrile musculocutaneous lymph node syndrome: clinical observation of 50 cases" in the "Japanese Journal of Allergy" in 1967. Thirty-five years later, Dr. Jane Burns of the "The University of California", San Diego, proposed his paper in English in the Pediatric Infectious Diseases Journal, bringing proper recognition to the paper from the West Coast (Kawasaki *et al.*, 1967). In 1970, Dr. Kawasaki succeeded in securing adequate funding to investigate the illness, leading to the establishment of the first diagnostic guidelines. The committee also encountered cases in which a coronary aneurysm was discovered during an autopsy that led to death. Better 2D echocardiography was introduced in 1976, which allowed for more significant advancements in that field. (Nakamura *et al.*, 2009)

KD is a global illness that has been reported in children from many ethnic backgrounds all over the world. KD is more prevalent in Asian nations like Japan, where the yearly prevalence rate increased from 239 points per 100,000 children in 2010 (Nakamura *et al.*, 2012) to 264 per 100,000 children recently (Harnden *et al.*, 2014). According to reports, KD incidence peaked in January and June /July and fell in October. In the US, the winter and early spring seasons were also the times when the disease's incidence peaked (Burns *et al.*, 2005). Moreover, children from Taiwan and Korea are more likely to contract the disease; 66 and 134, respectively, per 100,000 children under the age of five, have the condition in those two countries (Kim *et al.*, 2014; Lue *et al.*, 2007). Non-Asian nations show a much lower prevalence, in England, it is 8.39 per 100,000 children (Harnden *et al.*, 2009), while in Australia, it is 9.34 per 100,000 children under the age of five (Saundankar *et al.*, 2014).

Etiology and Pathophysiology:

Several theories have been proposed for the cause of KD. According to current theories, genetic predisposition and its interaction with an unidentified infectious cause may be predisposing factors to KD (Burns *et al.*, 1998). According to available data, genetic factors influence the development of KD more significantly. IgG receptor polymorphisms can make kids more susceptible to KD and raise their chance of getting a coronary artery aneurysm as shown in Figure 1. A robust genetic susceptibility based on ethnicity is also suggested by the higher prevalence of KD in Asian nations, such as Japan, Korea, and Taiwan, than in other countries outside Asia. In Hawaii, the incidence rate for Japanese American children was 210 per 100,000, while the incidence rate for Caucasian-American children in the same area was 13 per 100,000 (Uehara and Belay, 2012). The occurrence of KD was likewise linked to an infectious cause. Critical KD epidemics in Japan have demonstrated a particular origin in specific areas and a peak incidence in a particular month (Yanagawa *et al.*, 1999). The disease's sudden onset resembles the course of bacterial and viral infections. In 2013, Jaggi and colleagues expressed a possible relationship between an adenovirus infection and the development of KD (Rowley *et al.*, 2008). Some research has hypothesized that an inhaled virus may have been absorbed by tissue macrophages, resulting in the activation of innate immunity (Khor *et al.*, 2011; Onouchi *et al.*, 2013; Rowley, 2011).

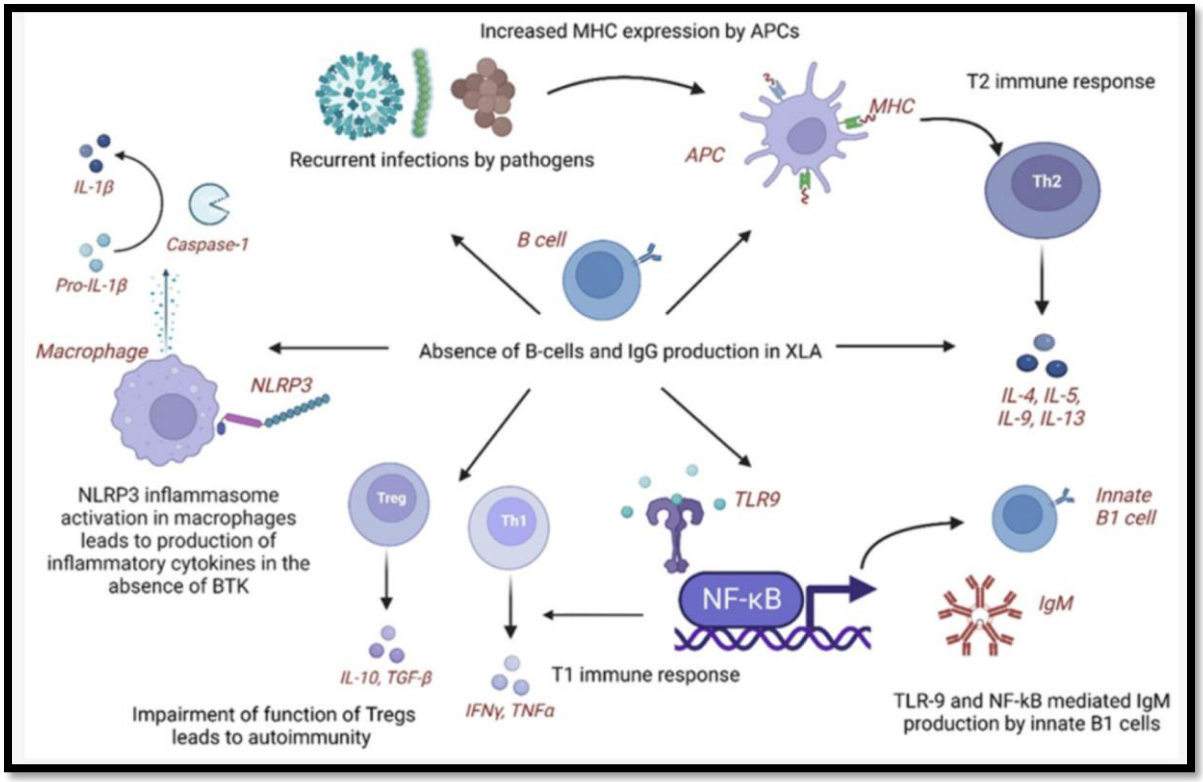

Fig. 1. Pathogenesis of Kawasaki disease in X-linked agammaglobulinemia including cellular and molecular mechanisms. Antigen-presenting cells, or APCs Bruton tyrosine kinase, or BTK; IFNγ: interferon γ; KD: Kawasaki disease; IL: interleukin; IgG: immunoglobulin G; IgM: immunoglobulin M; Key Histocompatibility Complex, or MHC Nucleotide-binding domain, leucine-rich containing family, pyrin domain containing-3 is known as NLRP3; Nuclear factor KB, or NF-kB. immune response of T helper type 1 (T1); immune response of T helper type 2 (Th2); Toll-like receptor-9, or TLR-9 Regulatory T cells, or "Tregs"; TNFα: tumor necrosis factorα; Th1: T helper type 1 cells; Th2: T helper type 2 cells; TGF-β: transforming growth factor-β; X-linked agammaglobulinemia

Diagnosis:

Clinical signs and symptoms are the primary means for diagnosing KD. In the US. In addition to fever that has persisted for at least five days. In 2004, The "American Heart Association" (AHA) developed an algorithm to assist in identifying patients who are at risk for the disease as illustrated in Figure 2 (Newburger *et al.*, 2004). It recommends using echocardiography and supportive laboratory testing to identify patients who are predisposed but do not fit all diagnostic criteria. Despite being referred to as "atypical" or "incomplete" KD patients, these individuals still have a chance of getting KD. According to an Australian study, this might happen in as many as 95.6 % of KD cases (Saundankar *et al.*, 2014). Inflammatory markers, anemia, leukocytosis, thrombocytosis, hypoalbuminemia, high liver enzymes, and potential sterile pyuria were among the suggested laboratory findings. Additionally, an echocardiogram can assist in excluding any possible early coronary artery involvement or abnormalities (Suzuki *et al.*, 2011; Hamada *et al.*, 2012). Drug sensitivity, "Stevens-Johnson syndrome", staphylococcal scalded skin syndrome, juvenile idiopathic arthritis, toxic shock syndrome, viral infections, and streptococcal scar fever are among the multiple differential diagnoses that are used to rule out KD (Burgner *et al.*, 2009; Kim *et al.*, 2011)

Biological testing is only sometimes required for diagnosis and is not

commonly done. Early diagnosis results demonstrate the destruction of the vascular media by neutrophils. Granulomatous inflammation is a hallmark of coronary arteritis, which appears 6–8 days after the onset of the disease and affects every layer of the vessel. Over time, lymphocytes, monocytes, and fibroblasts replacement and infiltration take place as the disease worsens, causing arterial remodeling (Lue *et al.,* 2007). RNA-contained cytoplasmic inclusion bodies are visible in 85 percent of acute and late-stage deaths when viewed under both light and electron microscopes (Burgner *et al.,* 2009).

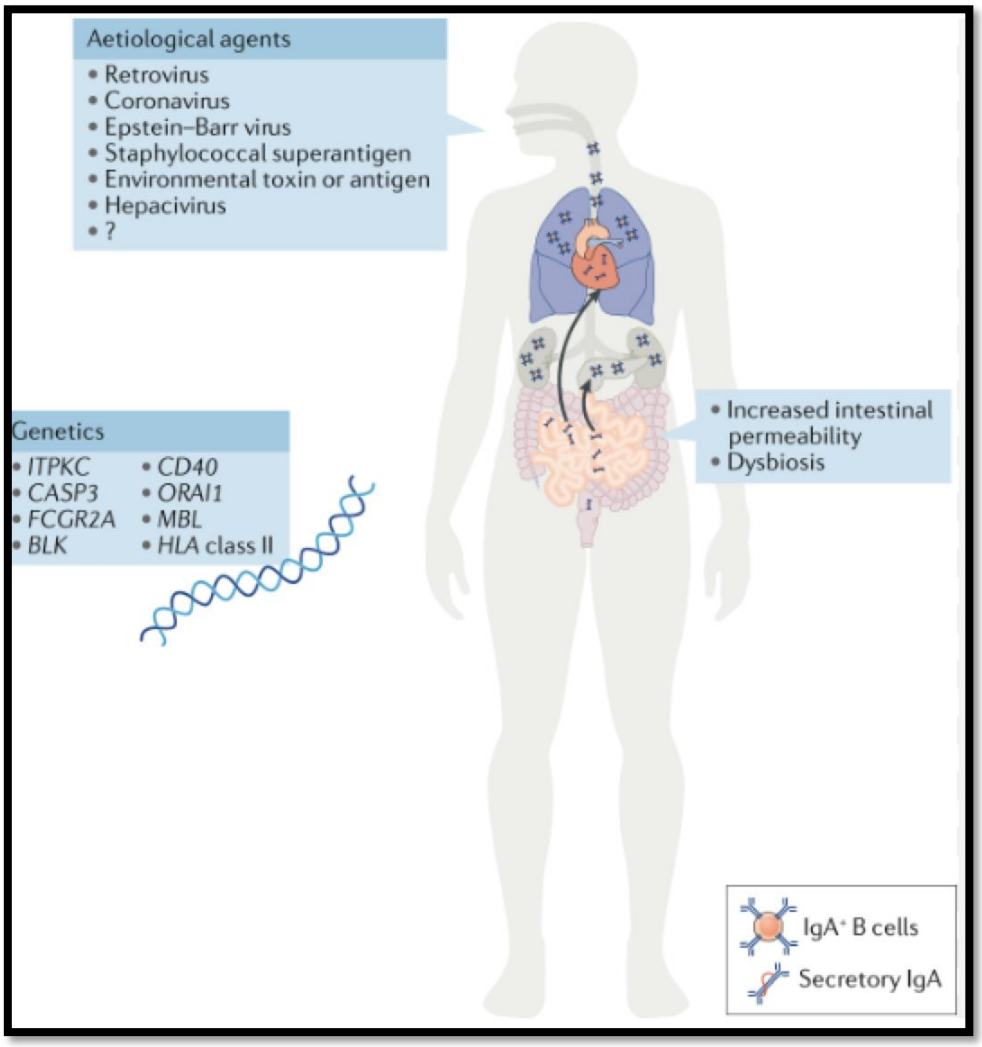

Fig. 2: Environmental and genetic risk factors of Kawasaki disease (Rivas and Arditi,2020).

Treatment:

"Intravenous immunoglobulin" (IVIG) and a high-dose of aspirin are used for KD treatment, despite some studies that have raised questions about the efficacy of aspirin in this regard (Lee *et al.,* 2013; Baumer *et al.,* 2006). According to a meta-analysis, starting treatment with corticosteroids in addition to IVIG reduces the risk of coronary artery abnormalities more effectively than starting treatment with IVIG alone (Chen *et al.,* 2013). If the case fulfills the clinical criteria for KD, it is strongly advised that treatment be started right away. Coronary artery aneurysm development can be stopped by IVIG. Numerous randomized controlled trials have provided evidence in favor of the administration and dosage of IVIG (McCrindle *et al.,* 2017; Newburger *et al.,*

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1991). Its effects are dose-dependent; a single 2 g/kg dose is given in the first ten days of the patient's illness or later if an echocardiogram reveals an aneurysm or other signs of inflammation. It can decrease the risk of coronary artery aneurysms from 25% to less than 5% and giant aneurysms to 1% (Newburger *et al.,* 1986). IVIG can affect the activity of T cells and decrease the production of cytokines and antibodies, which can lead to KD symptoms. It is thought that aspirin alters the inflammatory condition associated with KD and lowers the incidence of thrombosis. However, previous research has questioned the effectiveness of the use of aspirin in KD to stop the development of coronary aneurysms. The American Heart Association advises giving patients a high dose of aspirin, 80 - 100 mg per day, in four divided doses until they achieve inebriation (Sato *et al.,* 2013, Burns *et al.,* 2015).

Certain studies revealed that infliximab treatment resulted in a faster resolution than IVIG retreatment. However, in other studies, infliximab treatment reduced fever duration but did not show more improvement over IVIG and aspirin when used alone (Suzuki *et al.,* 1996). Antiplatelet medications or aspirin alone can be used to treat patients with mild to moderate aneurysms and refractory KD. Heparin and warfarin can be used to treat more giant aneurysms (Arend *et al.,* 1994). Methotrexate and cyclosporine A are two additional potential treatment options that have been suggested. The Ca2+/NFAT signaling pathway is the target of the calcineurin inhibitor cyclosporine A. It results in reducing the inflammatory response (Checkley *et al.,* 2015). In Japan, it has been applied as a third line of treatment in some KD cases (Kobayashi *et al.,* 2013). Polyglutamate metabolites may accumulate in the cells because of methotrexate (van der et al., 2014). The American Heart Association does not recommend its use in KD because its mechanism of action and its influence on KD are not fully declared (Lee *et al.,* 2008).

Prognostic Factors:

Studies involving Japanese children have identified several prognostic factors for coronary aneurysm development in KD patients. These factors include male sex, C-reactive protein (CRP) more than 200 mg/dl, age < one year or more than eight years, albumin less than 35 g/l, platelet count less than 35 × 104/mm3, delayed IVIG initiation, lower IVIG dose, and recurrent KD (Harada, 1991). According to a previous study, patients who are at risk of IVIG resistance can be identified using a scoring system. A score greater than 4 indicates a high risk of resistance, whereas a combined score of 0 to 3 predicts a low risk (Giannouli *et al.,* 2013).

Long-Term Follow-Up:

In the acute stage of the illness, the American Heart Association (AHA) recommends a baseline echocardiography examination. It is also advised to repeat the echocardiography in weeks two and six to eight following the illness (Kobayashi *et al.,* 2006). Frequent imaging is recommended if there are signs of poor recovery or high-risk factors. In addition, even in the absence of any abnormalities, the American Heart Association (AHA) recommended monitoring KD patients who are less susceptible and have no discernible coronary abnormalities for at least ten to twenty years after being diagnosed (Tremoulet *et al.,* 2014; Dietz *et al.,* 2017). If the aneurysm resolves by week six to eight in moderate-risk patients, they are considered low-risk patients. Regular cardiac evaluation every three to five years is recommended. Patients at high risk are more likely to experience a progression to coronary artery stenosis. It is highly advised to take warfarin or heparin along with antiplatelet therapy for an extended period (Seki *et al.,* 2011). Reduction of the myocardial oxygen demand by adding β-blockers is also possible. A comprehensive cardiac examination, electrocardiogram, and echocardiography should be carried out at least twice a year. A stress test and perfusion study are also recommended once

per year. Patients should be counseled to restrict their physical activity, considering their medical condition and bleeding risks. If more intrusive testing, like angiography, is required, it can be done for each individual patient (Manlhiot *et al.*, 2013).

Conclusions:

Although KD is still not fully understood, it is manageable using proper care and monitoring. Quick diagnosis and intervention can significantly enhance prognosis and reduce related complications. The fight against KD has a bright future with the recent developments in the diagnosis and treatment of the disease, such as the identification of NT-proBNP as a biomarker for early disease detection. The proper management of KD will continue to be guided by more explicit consensus as well as numerous published clinical experiences.

Declarations:

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