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Kawasaki disease: a review exploring the changes in etiology, epidemiology, and link to COVID-19

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ABSTRACT

Kawasaki disease (KD) is a condition that causes a systemic vasculitis in children primarily under the age of five. This study aims to review the changes in etiology, epidemiology and its possible link to COVID-19 since its characterization in 1967. This review was conducted by reviewing literature that explored causes, diagnostic procedures, treatment, epidemiology and links to COVID-19 by utilizing keywords such as Kawasaki disease, Covid-19, etiology, and epidemiology. Kawasaki disease's etiology has changed since its characterization credited to advancements in technology. Diagnostic procedures have become more efficient with a standard globally recognized criterion for the diagnosis of incomplete and complete KD. Treatment has remained relatively the same since its characterization, but it can defer on a case-to-case basis. KD etiologic agents have been studied however; the exact agent remains unconfirmed presently. However, the most popular theory is that KD is a combination of genetic as well as infectious causes. This is due to the seasonality seen in incidence of KD and that most cases occur in male children of Asian descent under the age of five. Kawasaki disease's link to the COVID-19 pandemic has been hypothesized and correlated with a 497% increase in KD cases since the viruses' emergence back in March of 2020. In conclusion, Kawasaki disease remains a condition of great mystery, with each advance comes another set of unanswered questions. The outlook remains dependent on honing in on its etiologic cause and improving treatments to limit the incidence of cardiac issues resulting from KD.

Keywords: *Kawasaki Disease, etiology, epidemiology, Covid-19*

INTRODUCTION

Kawasaki Disease (KD) is an acute systemic vasculitis that primarily affects children under the age of five (Han, 2000) Kawasaki disease is described as an autoimmune disease that attacks and inflames the medium sized vessels within the body, with a focus on the coronary arteries (Tang, 2020). The first case of KD was first encountered in 1961 by Dr Thomasau Kawasaki in Japan (Burns, 2000). It would later be described and recognized in 1967. The controversy behind the discovery of KD will be discussed later in the review. Although the exact cause of KD is unknown, the research discussed in this review will explore new theories that suggest that the causative agent could be an infectious agent that causes a specific immune response in genetically predisposed individuals.

KD is characterized by a fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy (Newburger, 2004). In severe cases, coronary artery aneurysms or lesions (CALs) as well as ectasia can develop, which can lead to ischemic heart disease or even death (Newburger, 2004). This sequela has been reported in 15-25% of untreated cases. However, new research has presented these symptoms in children that have been treated as well.

The criterion for diagnosis of Kawasaki disease has caused problems within the medical community because of the need for early diagnosis and treatment to prevent severe damage to the arteries and vessels. In the fifty-three years since the discovery of Kawasaki disease, it has now become the number one cause of acquired heart disease in children, passing rheumatic fever in the United States (Han, 2000). KD has also jumped back into the forefront of the medical community due to the ongoing COVID-19 pandemic. This literature review will explore how KD has evolved since its discovery in regards to its etiology, epidemiology, treatment, outlook, and its potential link to the COVID-19 pandemic.

CHANGES IN ETIOLOGY: CAUSE, DIAGNOSIS, TREATMENT

The first case of KD was reported in 1961 by Dr.Kawasaki in Japan (Burns,2000). The case involved a four-year-old male patient who was hospitalized and recovered from a "mysterious illness" with an unknown diagnosis. The emergence of KD can be seen as early as the 1950s, however knowing the existence prior to this time is unknown. At the time of its emergence, KD was described as a "non-scarlet fever syndrome with desquamation" (Burns, 2000). KD's description goes back to a case study of 50 patients experiencing this form of vasculitis published in 1967 by Dr. Kawasaki (Hedrich, 2018).

Since this first description, the criterion for

diagnosis of KD has vastly changed. Previously, a patient would have to display all the symptoms of KD in order to be diagnosed. Furthermore, there is no specific test to diagnose KD, but rather that other illnesses have to be ruled out in order to diagnose. This makes a swift and fast diagnosis even harder to achieve. However, in recent years patients have displayed a sort of range for KD starting from what is called “incomplete KD” to complete KD (Hong-Ryang, 2017). These ranges are based on clinical criteria that are now recognized globally. The classic or what is called complete KD is based on presenting four or more of the clinical features. The most common features of KD have been identified as a fever lasting more than five days, conjunctivitis, skin and mucous membrane affection, and cervical lymphadenopathy (Hedrich, 2018). The variance and latency of diagnosis with KD has proven to be a challenge. The longer it takes to confirm a diagnosis, the higher the incidence of complications with the coronary arteries. Late or missed diagnosis of KD has led to about a 25% incidence rate of coronary aneurysms or CALs in affected individuals (Hedrich, 2018).

Although, it is the same since discovery that no one diagnostic test can be used to diagnose KD, current research suggests that most cardiovascular manifestations are prominent in the acute phase. Most often this results in the child showing tachycardia, hyper dynamic precordium, a gallop rhythm, and depressed myocardial contractility that is second to myocarditis (Newburger,2004). These medical irregularities can be detected via EKG. Some other non-cardiac findings that aid in the diagnosis of KD are arthritis or arthralgia that can occur within the first week of the illness (Newburger, 2004). KD patients may also experience acute hearing loss accompanied by gastrointestinal problems such as vomiting and diarrhea. Some other laboratory findings include Leukocytosis. About fifty percent of patients have white blood cell counts above 15000/mm^3 (Newburger, 2004). Another study published in 2020 evaluated biological markers that would make the diagnosis and treatment of KD more effective. This study used bioinformatics data in order to identify three genes, CASP3, CD40 and TLR4 that could be possible diagnostic markers for KD (Tang, 2020). This research is the new focus point of being able to make more efficient and accurate diagnoses.

Incomplete KD or atypical KD is even harder to detect because these patients do not display the typical clinical features of the disease. Most often incomplete KD is diagnosed if the patient presents a fever lasting more than five days and at least 2-3 of the typical symptoms. The major problem that is still present in the diagnosis of KD, is that symptoms are often mistaken either for other diseases or for a reaction to antibiotics. For example, some children only present a fever and enlarged cervical lymph nodes. The rash and mucous changes that follow can often be mistaken as a reaction to antibiotics (Newburger, 2004). Some other symptoms presented can also be mistaken for viral meningitis. This risk is greatly increased when the patient is under one.

Since the discovery of KD, its cause or etiology has been a topic of controversy within the medical community. There is still no confirmed cause of KD, and its etiology remains a mystery. However, current research suggests a mixture of an infectious agent combined with genetic factors cause KD. At the time of discovery, KD was thought to be an Asian disease and be prevalent only in males under the age of five. This has proven not to be true, as KD is now present within every ethnicity as well as both genders. However, the incidence is still higher within the Asian community, which suggests that there is a genetic component to KD (Hedrich, 2018). Other evidence to suggest the presence of a genetic factor in KD is a case study that looked at a group of KD patients that all presented the same immunodeficiency (Rivas-Larrauri, 2019). The commonality between all the patients’ genetic codes suggested the presence of particular genes increased the risk of KD. These particular genes were CGD and XLA, which lead to the immune system being unable to eradicate the pathogens as well as an exaggerated inflammatory response (Rivas-Larrauri, 2019). This coincides with the theory that KD is a result of an infectious agent that produces an autoimmune response in genetically predisposed individuals.

There is also research to suggest the presence of an infectious agent, as the incidence of KD spikes seasonally in the winter/spring in most geographical areas (Burns, 2000). There has also been clear outbreaks with clear epicenters, combined with a peak incidence within the toddler age. This suggests a window of time where the body then builds antibodies to fight the effects of the infectious agent. The last commonality to suggest an infectious cause is that KD has similar symptoms to other infectious diseases (rash, fever etc.). Most current research further reiterates that the cause of KD is an infectious agent that causes a cascade effect on the immune system of genetically predisposed individuals. However, research now is primarily focused on identifying a diagnostic test for KD, instead of actually identifying a causative agent (Burns, 2000). This is in lieu of the fact that missed/late diagnosis increases the chance of major complications with the heart and of coronary aneurysms.

The treatment for KD has remained relatively constant since its discovery. Treatment for KD is subdivided into initial and long-term management. In the initial management phase, it is the priority to reduce inflammation within the body in order to reduce the risk of coronary artery abnormalities (Han, 2000). Standard initial treatment for KD involves a high dose

of IVGG (single dose of 2g/kg) therapy which has proven to be the most effective in preventing cardiac complications (Han, 2000). Thus, IVGG therapy remains the cardinal treatment for the management of KD. In most cases, patients respond to IVGG and are able to be discharged with minimal complications.

The long term management of KD is determined by the degree of coronary artery involvement. If treatment failed in preventing CALs or aneurysms, further treatment will be needed for the individual.

Most cases involve a taper of low dose ASA therapy, and regular electrocardiograms with stress testing, especially for children under the age of ten (Han, 2000). However, if the aneurysm begins to cause an obstruction, routine electrocardiography combined with both stress testing and angiography is recommended (Han, 2000). Thus, it is imperative that a quick diagnosis be made in order to start treatment to greatly reduce the risk of cardiac complications. These complications have been mostly seen in older children between the ages of three and five because of the less frequent occurrence of KD between these ages.

However, advancements in technology and research have brought forth a new possible treatment to use in conjunction with IVIG in order to treat KD. A new study proposed using adjuvant herbal therapy in order to treat the disease (Tang, 2020). Adjuvant therapy refers to a substance that enhances the immune response to an antigen. For example, resveratrol from *Vitis vinifera* L., a type of fruit was used to treat patients with KD and found to possess anti-inflammatory properties on human coronary artery endothelial cells (Tang, 2020).

Another facet to note when it comes to the treatment of KD is IVIG resistance. New studies have shown that anywhere between 6.7 to 26.8% of KD patients have experienced IVIG resistance (Lin, 2017). IVIG resistance increases the chance of cardiac complications, and with no way to test if a patient will be resistant it becomes an instance of trial and error. The causes of IVIG resistance are currently unknown, however it is suspected that the chances of resistance increase with younger patients, delayed initial treatment, and brand of IVIG (Lin, 2017).

CHANGES IN EPIDEMIOLOGY

Kawasaki Disease first emerged in Japan and was previously thought to be an “Asian” disease. At the time of its emergence, it was almost exclusively described in Japan and other parts of Asia. KD was commonly thought to be disease that primarily affected children under the age of five and mostly occurred in males. However, as previously stated KD has now become the leading cause of acquired heart disease in children in the United States (Newburger, 2004). KD can now be seen across every country and affect every ethnicity as well. This trend has been a result of a change of incidence and distribution of cases all over the world. KD first emerged in the United States, in Hawaii simultaneously as it was first being described in Japan (Burns, 2000). The incidence of KD has increased since its emergence, however, initially outbreaks of KD occurred in nationwide epidemics, whereas now they occur in limited regional epidemics (Burns, 2000). Three major epidemics were recorded in Japan in 1979, 1982, and 1986 (Uehara, 2012). Another nationwide epidemic has not been observed nor recorded since 1990 globally, yet the incidence of KD has more than doubled during the last two decades (Uehara, 2012).

The highest incidence rate to this date was recorded back in 2008 in Japan with 218.6 children per 100,000 under the age of five. KD is found to occur all over the world, however the highest incidence of the disease remains in Japan with about 5000-6000 new cases diagnosed per year. Males remain at a higher incidence rate than females occurring at a ratio of about 1.5 to 1 (Burns, 2000). In the United States, KD occurs in about 4 to 15 children per 100,000 under the age of five. The highest incidence rate occurs in the northeast region of the country (Uehara, 2012). Furthermore, incidence occurs among all ethnicities, however a higher incidence is seen with the Asian American population. Several countries including Japan, Taiwan, India, USA, and Canada have also reported a seasonality with cases of KD (Ling, 2017). Across the board more cases of KD were reported January through March at about 40% higher than the rest of the year (Lin, 2017). KD presently is increasing in number since its emergence and with the current COVID-19 pandemic, there has been spikes in the number of cases reported globally.

CONNECTION BETWEEN COVID-19 AND KD

Covid-19 emerged as the newest strand of the coronaviruses (SARS-CoV-2) that has proven to be more infectious than the seasonal flu, while also causing more severe side effects in certain groups of people. Covid-19 is a virus that attacks the upper respiratory system and has become one of the most infectious viruses of the modern age. Currently, Covid-19 cases are still rising globally and the implications of long term health are still being evaluated. The pandemic has been on the rise since March of 2020 to present day. Most commonly, the virus is known to cause more severe side effects in individuals over the age of 65 or individuals that have a preexisting condition such as heart disease, diabetes or those who are immunocompromised. Covid-19 effect on children and younger populations has been minimal overall, however an association between the virus and a rise in the number of KD cases has been seen (Viner, 2020).

Clusters of patients from all over the world have been diagnosed with KD or shown symptoms very similar to that of KD since the outbreak of Covid-19 (Viner, 2020). Furthermore, in France, one of the epicenters for the virus, 17 cases of KD were diagnosed within 11 days compared to the average of 2 cases per month diagnosed between 2018-2019 (Moreira, 2020). Furthermore, out of those 17 cases, 82% of the children also showed IgG antibodies for the coronavirus suggesting an association between the virus and KD. An important note is that globally the spike of KD cases was seen mostly in children of sub-Saharan African or Asian descent, reiterating the belief that KD has a genetic component (Viner, 2020).

Another study conducted in France examined the association of the virus with cases of KD two weeks after the peak of Covid-19 cases back in March. Researchers were able to identify a 497% increase of KD cases following the peak number of Covid-19 cases with about 230 children diagnosed (Ouldali, 2020). This increase of KD cases was also consistent with another spike of KD cases that occurred back in 2009 during the H1N1 pandemic (Ouldali, 2020). In this study, researchers also identified other viral respiratory illnesses that have become triggers for the onset of KD (Ouldali, 2020). This pattern coincides with the standing theory that KD is caused by an infectious agent. Another important note is that Covid-19 has been proven to have an association with not only causing incomplete and complete KD, but also myocarditis and toxic shock syndrome (Ouldali, 2020). Although, the overall impact of Covid-19 on children is minimal, the belief that the virus can cause a higher incidence of KD is important. The ability to make more efficient and accurate diagnoses is vital in preventing life-long and life-threatening damage to the arteries of the heart that are increased with failure to diagnose KD early. Furthermore, the link between upper respiratory viruses and the incidence of KD in history may provide more insight into its etiology and ways to prevent KD from happening.

CONCLUSION

In conclusion, Kawasaki disease remains a disease of great mystery. The clinical diagnostic procedures for KD have vastly improved as the knowledge of the disease has become more widespread. Kawasaki disease was once unheard of and very rare to see, but with the advancement of technology and sharing of information it is easier to recognize and treat. However, the need for more efficient diagnoses are needed in order to decrease cardiac complications. The etiologic agents that cause the sudden inflammatory response remain only theories that are heavily supported and theorized, however none have been confirmed. The leading theory remains that the cause of KD is a combination of infectious and genetic components. The treatments for KD have remained constant yet new cases with complications to IVGG therapy prove to be challenging as most treatments then differ on a case-to-case basis. Currently, KD has become a hot topic brought forth by the current Covid-19 pandemic. The future and outlook of KD is dependent on further research into its etiology and treatments in order to prevent severe coronary artery damage. With the current Covid-19 pandemic, medical professionals should be aware of the spike of KD cases and work to quickly diagnose and treat KD to limit the risk of coronary artery damage.

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