The New Relationship between Kawasaki disease and MIS-C

Abstract

Kawasaki disease (KD) is a childhood disease associated with serious coronary artery complications. It is the most common cause of pediatric acquired heart disease in developed countries and is increasingly reported from many developing countries. The etiology of KD is still uncertain; interaction between a genetic predisposition and several environmental and immunological factors has been hypothesized. The Centers for Disease Control and Prevention reported that many children with MIS-C were infected with the new coronavirus or had close contact with people with the new coronavirus. Children with MIS-C show symptoms similar to severe cases of Kawasaki disease. An early discussion of similarities and differences between the novel coronavirus and Kawasaki disease was initiated towards the end of March 2020 between Dr. Karim Elakabawi, Benha university, Egypt; Prof. Manuel Katz, the chairman of the global CIP, Israel; and Prof. Jiao Fuyong, the head of the Center of Kawasaki disease diagnosis and treatment, shaanxi province, China. The three doctors discussed their strong observations about the epidemiologic distribution of KD cases and global affection of the Corona viruses family: SARS, MERS, and the most recently COVID-19. This article mainly summarizes the similarities and differences between KD and MIS-C.

Key words:

Kawasaki disease (KD) COVID-19 Children's Multiple System Inflammatory Syndrome(MIS-C) similarities differences

Introduction

Kawasaki disease is also known as mucocutaneous lymph node syndrome. Typical clinical manifestations include persistent fever (more than 5 days), pleomorphic rash, non-purulent conjunctival hyperemia, oropharyngeal mucosal hyperemia, swelling of the limbs, desquamation near the fingers or toes, and Suppurative cervical lymphadenopathy and coronary artery disease. KD is generally self-limiting. It is estimated that about 20%-30% of untreated patients will eventually develop severe vascular complications such as coronary artery dilation, coronary

artery stenosis, or coronary artery fistula[1].So far, the exact cause of KD is still unclear. According to the seasonality of its onset and the usual history of infection 30 days before diagnosis, it is speculated that it may be related to viral infection[2]. However, more and more evidence supports that genetic factors play a key role in its occurrence and development. A large number of evidences show that the incidence of KD is increasing in certain groups of people. Many genes are involved in the development of Kawasaki disease and the development of complicated coronary artery lesions: for example, ITPKC, CASP3, TGF-s, BLK, CD40, FCGR2A, KCNN2, PECAMP-1, NMNA, etc[3].

Children's Multiple System Inflammatory Syndrome (MIS-C) refers to the swelling of organs including the heart, lungs and kidneys. The Centers for Disease Control and Prevention reported that many children with MIS-C were infected with the new coronavirus or had close contact with people with the new coronavirus.The patient developed MIS-C symptoms after being infected with COVID-19, including fever, abdominal pain, and inflammation. The inflammation manifested as diffuse rash, conjunctivitis, and swelling. In more severe cases, multiple organ dysfunctions may occur, including respiratory distress, hypotension, liver and kidney damage, and changes in mental status.Because the symptoms are very similar to the "children’s heart killer" Kawasaki disease, some doctors call the children’s strange disease quasi-Kawasaki disease. There are articles reporting that perineal desquamation is an early clue to the KD phenotype of MIS-C[4]. Findings of the present systematic review show that the incidence of KD-like syndrome in the COVID-19 pandemic increased significantly[5].The emergence of patterns that seem quite similar in several cities certainly points to a causal association between COVID-19 infection and KD.

The two epidemiologic similarities between the two diseases :

Regional distribution

The global epidemiologic distribution of KD mimics the pattern of which Corona viruses spread to the world. Both diseases first recognized in East Eastern countries then increasing numbers and severe affection are mainly reported from developed countries in western Europe and USA. The theory behind KD distribution is thought that the disease is affected by genetic susceptibility and environmental factors like air pollution and increased industrialization that favor its

prevalence in the more developed countries. The highest rates of KD affected children are reported from East Eastern Asian countries followed by Western Europe and North America, with increasing numbers started to be reported from rapidly developing countries as India, South America, and some middle Eastern countries like Turkey and Iran. KD is rare in sub-Saharan Africa, middle Asia, and the remaining middle Eastern countries (Figure 1).

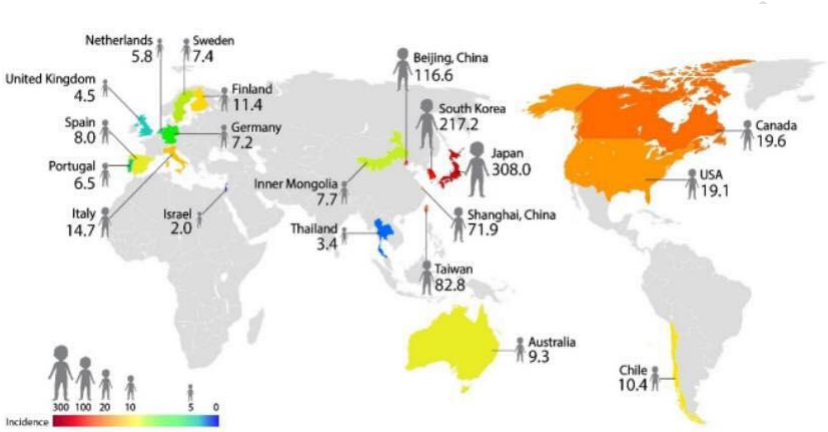


Figure 1 KD in sub-Saharan Africa, middle Asia, and the remaining middle Eastern countries

On the other hand, The Corona Viruses SARS and COVID-19 the initial focus was in China, then spread mainly to Western Europe and north America. However, in last weeks the number of Covid- 19 cases start to rise in less developed and developing countries. This distinctive pattern of disease propagation was hypothesized to be because of people's mobility and traveling along commercial airline routes[6].

Of note, the severity of cases and mortality rates of COVID-19 up till now is much lower in middle Eastern and sub-Saharan African countries compared to European countries, for example for the date 6th of May 2020, the total reported cases in Saudi Arabia and Qatar are 30,251 and 17,142 patients, respectively with reported mortality rates of 0.7% and 0.07% respectively. When these numbers are compared with European countries with similar reported total number of cases like Switzerland (30,009 patients) and Ireland (21,983 patients), they report mortality rates of about 6%. In 2003, also the outbreak of SARS infection had almost no effect on the middle eastern and African countries.

seasonal pattern

KD has a defined seasonal patterns in the extra-tropical latitudes of the Northern Hemisphere characterized by a peak of reported cases occurring in winter season starting in January through

March[7]. The corona viruses also appear to be linked to the winter and cold seasons. The SARS-CoV appeared in November 2002 in the Guangdong province of southern China , and declined suddenly by July 2003. The new COVID-19 virus was first reported in December 2019 in Hubei Province, China and massively spread globally since late February 2020.

The other similarities between the two diseases :

Pathogenesis

The specific cause of MD is not clear, but it is currently found to be related to viral infection and genetic susceptibility, which causes excessive immune response and platelet activation, which in turn leads to changes in systemic small blood vessel inflammation, which manifests as multiple organ damage, including coronary artery damage. Studies have pointed out along with platelet number, platelet activation may be a major determinant of various complications associated with KD, which confirms the rationale of antiplatelet therapy in KD[8]. some findings suggest that most enriched innate immune response pathways were shared between transcriptomes of KD and COVID-19 with moderate severity. Geneticpolymorphisms associated with innate immune dysregulation and KD susceptibility, together with variants in STING and STAT3, might predict COVID-19 severity and potentially susceptibility to COVID-19 related MIS-C[9]. some studies further suggest that rare inborn errors of immunity (IEIs) altering the immune response to SARS-CoV-2 may underlie the pathogenesis of MIS-C in some children. The discovery of monogenic IEIs underlying MIS-C would shed light on its pathogenesis, paving the way for a new genetic approach to classic KD, revisited as a heterogeneous collection of IEIs to viruses[10].

Clinical manifestations

MIS-C and KD both involve hyperinflammatory responses,presenting clinically with persistent high fever, often accompanied by a visible rash and conjunctivitis. These two conditionsremain elusive. They appear to be related but different conditions, with a clinical and immunological overlap (Figure 2)[10]. The specific manifestations of MIS-C are: fever, rash, vomiting, neck lymphatic enlargement, chapped lips and diarrhea, etc., similar to the clinical features of KD.

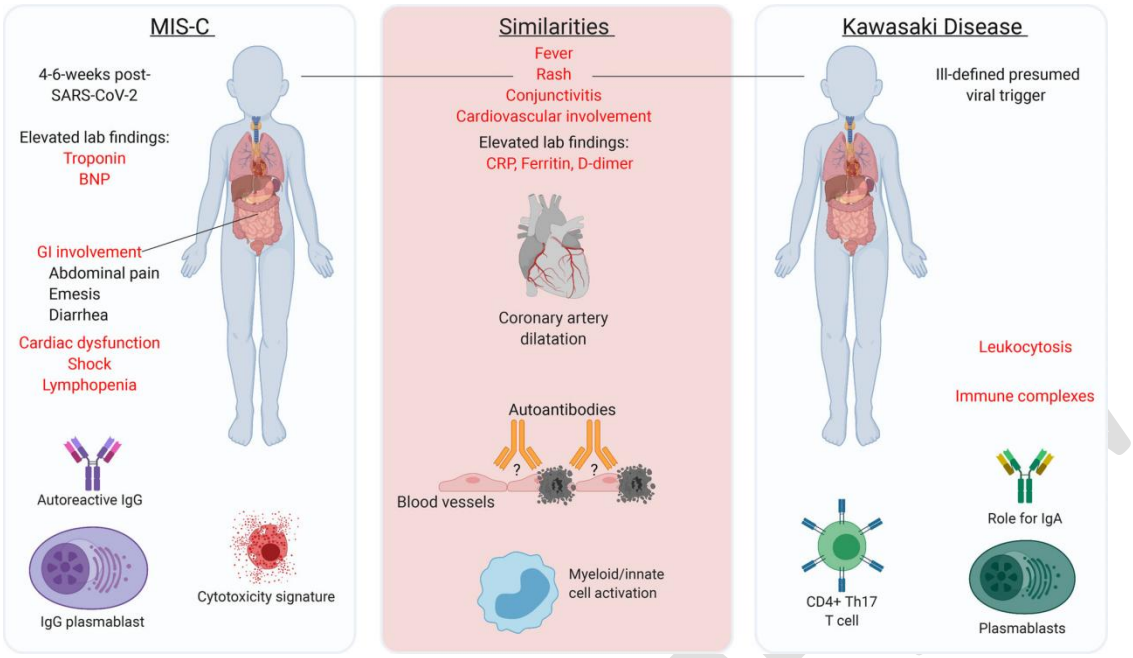


Figure 2[10]. A comparison of MIS-C and KD. The common and different clinical and immunological features of MIS-C and KD are shown. The major characteristic similarities or differences between the two conditions are highlighted in red. Th17, T helper type 17 cell.

The differences between the two diseases:

The multisystemic inflammatory syndrome in children (MIS-C) related to the SARS-CoV-2 pandemic (also termed Kawasaki-like disease, or Kawa-COVID-19) appears to share clinical, pathogenetic and laboratory features with KD. But at present, there are also many differences between the two diseases. An article pointed out[11] that the most important difference between MIS-C and KD is the older age of onset, more frequent gastrointestinal involvement, myocarditis and/or cardiogenic shock and heart failure requiring positive muscle support, circulatory assistance, and PICU admission . In addition, MIS-C may be resistant to IVIG infusion therapy. MIS-C is a cytokine storm driven mainly by IL-6 and IL-8, and in KD patients, IL-1 seems to be the main mediator of coronary artery inflammation. An article reported[12] three cases of KD-like cases that occurred in severely affected areas in northern Italy during the SARS-CoV-2 pandemic, manifesting as persistent fever, diarrhea, elevated inflammatory markers, and myocardial damage. An article pointed out [13]that about two-thirds of COVID-19-related KD children have been admitted to PICU. In addition, about a quarter of people need mechanical ventilation/intubation, and even some of them need to be readmitted to the hospital. In general, MIS-C is in a serious condition.

There is a more pronounced difference between the two extreme manifestations of Kawasaki disease shock and MISC shock. Both patient populations who experienced shock showed elevated levels of CRP and ferritin, but the laboratory abnormalities shown in MIS-C shock cases were more pronounced. In MIS-C, the ethnicity of the patient population is mainly African-American/Hispanic, while the KD patients who experience shock are more Asian[14]. There are some other differences see chart (Figure 3)[14].

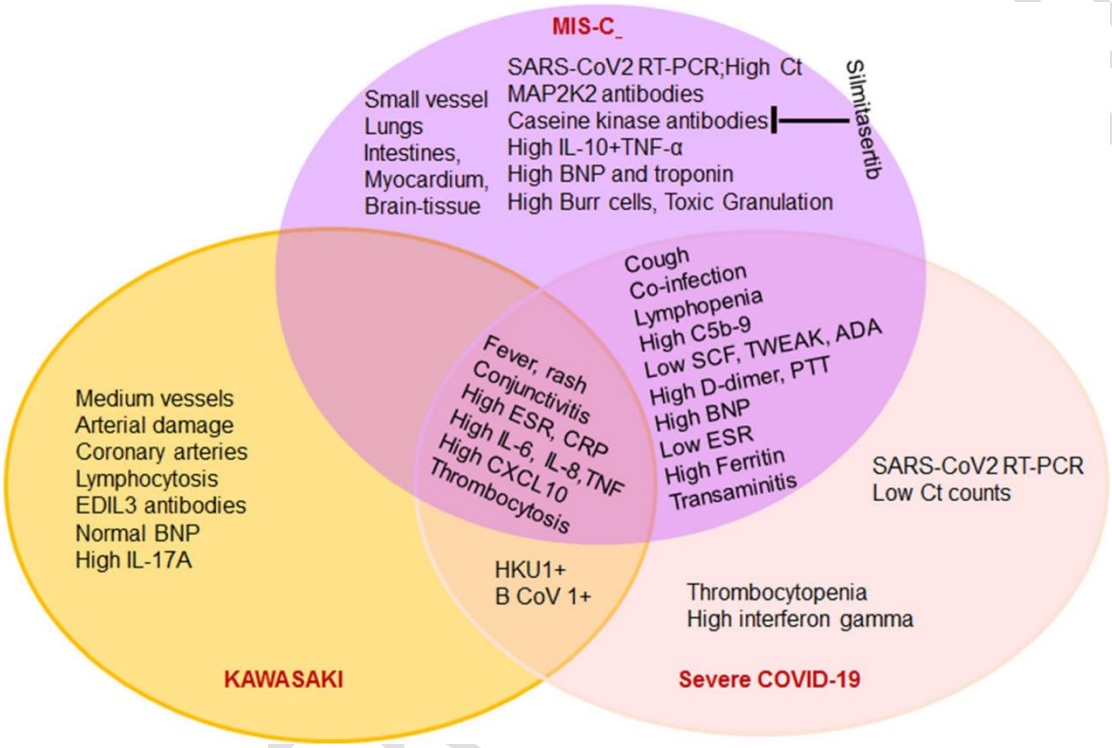


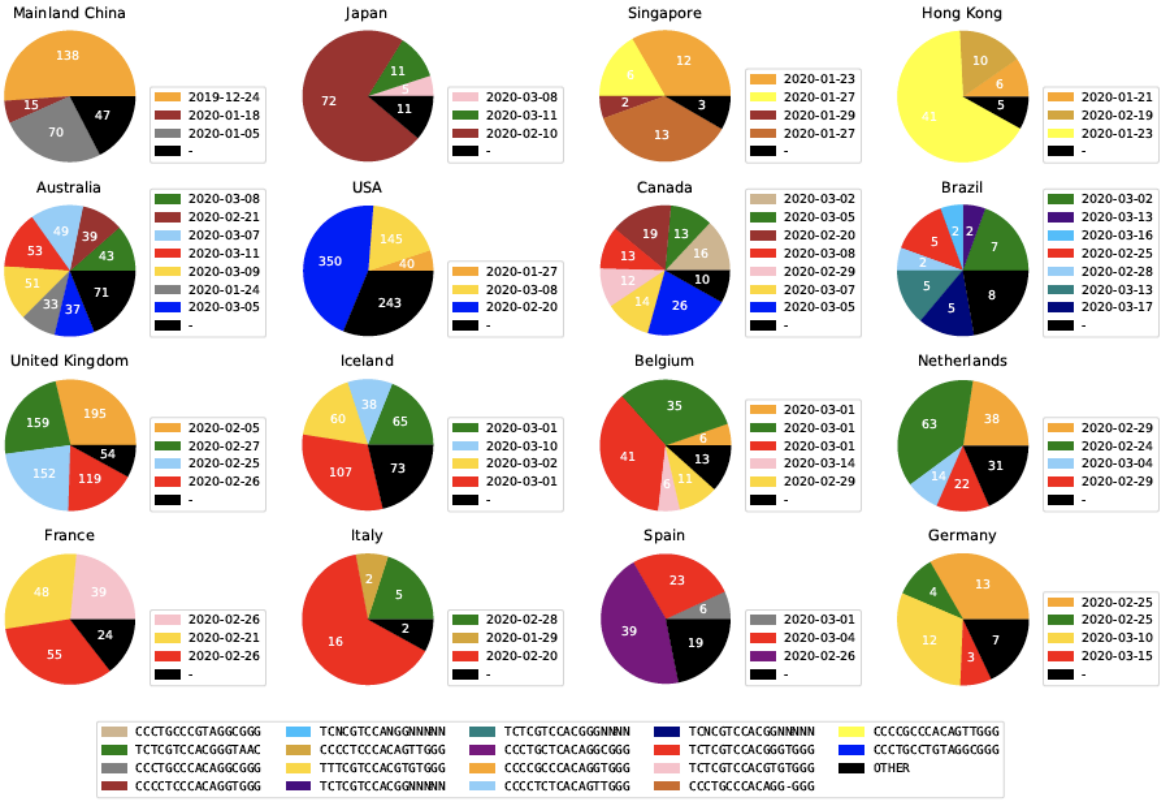
Figure 3 KD fever variation

A key distinguishing feature between the classic KD and the current virus-related hyperinflammatory syndrome is their platelet count. MIS thrombocytopenia, KD thrombocytopenia. One possible explanation for this is that their underlying immune pathogenesis is different[15]. Notable features of Kawasaki disease-like disease associated with SARS-CoV-2 include older age, more frequent sub-Saharan African descent, gastrointestinal involvement, shock, myocarditis, lymphopenia, and higher levels of inflammatory markers. This is the difference from KD[16]. This COVID-19-related syndrome seems to have a greater impact on older children, with a higher rate of heart involvement, and more severe conditions that require ICU management[17]. Unlike KD, the guidance statement does not recommend immunomodulatory treatment for most pediatric patients who usually develop mild or moderate

COVID-19. For children with severe or critical illness, the use of immunomodulators may be beneficial[17,19].

Discussion

The similarities of both diseases are raising several questions that would help better understanding and managing both. The aetiology of KD is still unknown, it is believed to be a result of adverse immune response to an environmental trigger believed to unknown viral infection occurring in genetically susceptible patients. Interestingly in the last two weeks a growing number of hospitals in the U.S., U.K. and other European countries have reported several cases of children with Kawasaki-like symptoms that is believed to be related to the recent COVID-19 infection. KD mainly affects children under 5 years old and is thought to be due to hyperimmune response to unnoticed infection. Corona viruses showed sparing to children or cause few symptoms and signs, but the recent reports of children with documented COVID-19 and Kawasaki- like characteristics may raise concerns about the true effects on pediatrics populations. Treatment of KD patients with intravenous immunoglobulin (IVIG) within 10 days after disease onset can lower the incidence of serious coronary complications from 25% to <5%. Similarly, if this theory is true, the complications of COVID-19 resulting from hyperimmune response in some patients may be better managed if IVIG is considered early in the course of treatment. Lastly, thinking about what causes Atypical Kawasaki syndrome in Australia, UK, and middle east, and not in China where KD is endemic? The reason probably is related to the genetic code of the virus that changes during replication and spread around the planet. Similar to the detected different COVID-19 virus subtypes that cause different clinical features and severity in different regions(Figure 4)[18]. There are many similarities between the two diseases, but the current findings are also different. In the future, more research is needed to better guide clinical treatment to achieve better treatment effects and prognosis.



(Figure 4)[18]Major SARS-CoV-2 genetic subtypes in countries/regions with the most sequences (indicating date subtype was first sequenced in that country/region). Subtypes with less than 5% abundance are plotted as "OTHER."

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