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Review

A comparison of Kawasaki Disease and multisystem inflammatory syndrome in children

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ABSTRACT

Background: Due to the COVID-19 pandemic a novel disease has emerged, multisystem inflammatory syndrome in children (MIS-C). It presents post virally after a COVID-19 infection, and its clinical presentation and symptoms are very similar to Kawasaki Disease (KD).
Aim of review: The objective of this review is to compare and contrast differences of Kawasaki Disease and MIS-C.
Key scientific concepts of the review: Kawasaki Disease and MIS-C are very similar in clinical presentation and symptomatology. Understanding the diagnostic criteria is crucial to making an accurate diagnosis. Treatments in Kawasaki Disease are established, while in MIS-C treatment protocols are continuing to develop. Careful history taking and laboratory marker analysis should guide the clinician to accurate diagnosis.

1. Background

As the COVID-19 pandemic has spread across the globe, a novel disease, multisystem inflammatory syndrome in children (MIS-C), has also emerged. The presenting symptoms and clinical course have been compared to Kawasaki Disease (KD). This review is aimed at providing information to assist clinicians in differentiating between these diseases.

2. Methods

A non-systematic review of the current literature on MIS-C and Kawasaki Disease.

2.1. Epidemiology

Kawasaki Disease predominantly affects children between 0 and 5 years of age but can occur in older children [1]. In 2016 the Center for Disease Control (CDC) reported there were 5440 hospitalizations due to Kawasaki Disease, with approximately 60% of children under 5 years of age [1]. Females are affected 2/3 less frequently than males, and infants less than 4 months of age are rarely affected [2]. The prevalence is highest in children of Japanese and Asian descent compared to other areas of the world [2]. In the United States, the incidence is thought to be 25 in 100,000 patients ages 0–5 years [2,3]. In Japan, the incidence is approximately 243.1 per 100,000 patients ages 0–5 years [2,3].

The exact incidence for MIS-C is currently unknown, with one published study estimating the incidence to be 5.1 out of 100,000 children, with an average age of 8 years [4]. Other reports suggest that it occurs in less than 1% of confirmed childhood COVID-19 cases [5]. In 2020, the CDC released data that of 1097 cases of MIS-C, 3/4 patients were Hispanic or African American children, with the average age at diagnosis being 8 years [6]. Of the 1097 cases of MIS-C, 20 resulted in death [6].

2.2. Immune response/pathophysiology

While the exact cause of Kawasaki Disease is not known, it is postulated that it may be caused by a prior viral infection which results in an acute vasculitis that affects medium sized arteries including the coronary arteries [7,8]. Immune complexes are formed that signal the proliferation of monocytes and macrophages resulting in neutrophilia [9]. The severe inflammation caused by the immune complexes triggers a cytokine release that results in organ injury. The same signals produced by immune complexes also trigger a reactive thrombocytosis, elevating the platelet count [10]. Apart from the immune complex reactions, research has also shown that immunoglobulin A (IgA) plays a role in Kawasaki Disease and that elevated IgA levels correlate with coronary artery involvement [9].

With MIS-C, COVID-19 viral particles which exist after the virus has

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been shed reside within infected tissue including myocardial cells [6]. The viral particles lead to a form of molecular mimicry that result in a hyperinflammatory immune response. The activation of monocytes and macrophages leads to neutrophil predominance, and the inflammation and cytokine release causes cardiac damage [6]. In MIS-C, the inflammation occurs as the immune system attempts to eradicate viral particles from the body. Interferon-gamma (IFN-g) activation results in increased human leukocyte antigen (HLA) presentation in tissues leading to a more "sensitized" immune response [6]. The Interleukin-1 (IL-1) and IFN-g pathway activation lead to cluster of differentiation 8 (CD8) cytotoxic T cells response that migrate to the heart and other organs, damaging the tissue where the virus resides [6]. The release of inflammatory mediators that stimulate CD8 cytotoxic T cells also cause viral suppression of the bone marrow and activation of platelets [10].

Studies of both Kawasaki Disease and MISC show increased Interleukin-1, Interleukin-6, and Interleuki-18 secretion as well as signaling in tumor necrosis factor (TNF) and IFN-g pathways that cause the release of various cytokines that lead to cytokine storms [3,6,11].

2.3. Diagnostic criteria

Patients presenting with Kawasaki Disease and MIS-C can have similar symptoms, physical findings, and lab results, but they have different diagnostic criteria. Understanding these differences is an important first step in differentiating between the two illnesses. Definitions/diagnostic criteria of Kawasaki Disease, atypical Kawasaki Disease, and MIS-C are outlined in Table 1 [12,13].

2.4. Organ system involvement and clinical presentation

2.4.1. Cardiovascular

Kawasaki Disease (KD) is a leading cause of acquired heart disease in the United States [1]. The main complication of Kawasaki Disease, particularly if untreated, is the development of coronary artery aneurysms [7]. Although the exact mechanism for aneurysm formation is unknown, it is likely related to immune complexes triggering inflammation [10]. Proposed pathological processes leading to coronary aneurysms in Kawasaki Disease include necrotizing arteritis with neutrophilic responses, subacute or chronic inflammation of the arteries with migration of various leukocytes to the arterial wall and proliferation of the arterial lumen tissue triggered by inflammation [3]. Intravenous immunoglobulin (IVIG) blocks immune complexes that develop in Kawasaki Disease which reduces damage to the epicardium and risk of coronary artery aneurysms [10]. Persistent inflammation can also put a Kawasaki Disease patient at risk for myocarditis, and pericarditis [3].

The most common cardiovascular complication in MIS-C is ventricular dysfunction, but coronary artery dilation or aneurysms and pericardial effusions can also occur [14]. In a study of 503 patients hospitalized with MIS-C, 34.2% had decreased left ventricular function with decreased left ventricular ejection fraction. For most patients, the ventricular dysfunction is mild and recovers quickly with treatment [15]. Elevated brain natriuretic peptide (BNP) and high troponin levels are also common findings in MIS-C [15,16]. Severe MIS-C can lead to hypotension and hemodynamic instability causing cardiogenic and/or distributive shock [17]. These patients may require administration of vasopressors and in rare cases extracorporeal mechanical ventilation (ECMO) [17].

2.4.2. Pulmonary

Pulmonary symptoms are usually absent in Kawasaki Disease. Post viral cough and congestion may be present, but pulmonary involvement during the acute phase of Kawasaki Disease is rare [3].

With MIS-C, respiratory involvement usually consists of respiratory insufficiency, pleural effusions, and pulmonary infiltrates responsive to supplemental oxygen, although some patients can progress to needing invasive respiratory support [17].

Table 1
Diagnostic criteria for typical and atypical Kawasaki Disease and MIS-C.

Kawasaki Disease	Illness in a patient with fever of 5 or more days duration (or fever until the date of administration of intravenous immunoglobulin if it is given before the fifth day of fever), and the presence of at least 4 of the following 5 clinical signs: • Rash • Cervical lymphadenopathy (at least 1.5 cm in diameter) • Bilateral conjunctival injection • Oral mucosal changes • Peripheral extremity changes
Atypical Kawasaki Disease	Patients whose illness does not meet the above KD case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete KD: Criteria is as follows: Fever for 5 days or more meeting 2 to 3 diagnostic criteria or infants with fever for 7 or more days with no other explanation: - If the C-reactive protein (CRP) is <3 mg/dl and erythrocyte sedimentation rate (ESR) < 40 mm/h, conduct serial clinical and laboratory assessments if fevers persist. If peeling begins an echocardiogram is then indicated. - If the CRP is 3 mg/dl or more and ESR is 40 mm/h or more, and there are 3 or more of the following laboratory findings: 1) Anemia for age 2) Platelet count of 450,000 or more after the 7th day of fever 3) Albumin of 3 g/dl or less 4) Elevated Alanine Aminotransferase (ALT) 5) White Blood Cell count of 15,000 mm^3 or more 6) Urine White Blood Cells of 10/hpf or more or - Positive echocardiogram Treatment is then indicated [3]
Multi-inflammatory syndrome in children related to COVID-19	An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND: • No alternative plausible diagnoses; AND • Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. *Fever ≥38.0 °C for ≥24 h, or report of subjective fever lasting ≥24 h **Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin Additional information: Some individuals may fulfill full or partial criteria for Kawasaki disease should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection [13]

Information for MIS-C and Kawasaki disease in this table was obtained from the center for disease control website.
https://www.cdc.gov/kawasaki/case-definition.html.
https://www.cdc.gov/mis/mis-c/hcp/index.html.
Information on atypical Kawasaki disease algorithm is from: McCrindle BW,

Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. doi: https://doi.org/10.1161/CIR.0000000000000484.

2.4.3. Gastrointestinal

Initial symptoms of both Kawasaki Disease and MIS-C can include vomiting, abdominal pain, and diarrhea. Gastrointestinal symptoms tend to be more prevalent in MIS-C compared to Kawasaki Disease, possibly due to increased viral load in tissues of the gastrointestinal tract [15]. In one study of MIS-C patients, gastrointestinal involvement was the second most often involved organ system behind the cardiovascular system [15]. The gastrointestinal symptoms of Kawasaki Disease usually occur before the hallmark signs of Kawasaki Disease appear which can lead to delayed diagnosis and treatment [18].

2.4.4. Hematological

Hypercoagulable states occur in both Kawasaki Disease and MIS-C but are more common in MIS-C. These can lead to complications including deep venous thrombosis and pulmonary embolism. As a result, many patients with MIS-C are treated with anticoagulation including aspirin and enoxaparin [17]. In the setting of Kawasaki Disease causing significant coronary artery aneurysms (internal luminal diameter possessing an absolute diameter of >8 mm or a Z score of 10 or more), antiplatelet and anticoagulation therapy is recommended. The use of high dose aspirin paired with warfarin, or enoxaparin is a common treatment in the setting of significant coronary aneurysms [3].

2.4.5. Mucocutaneous/dermatological/lymphatic

Hallmarks of Kawasaki Disease include a maculopapular rash, mucocutaneous ulceration including cracked red lips, and a strawberry red tongue. Erythema of the palms and soles of the feet and edema of the hands and feet are common [16]. Cervical lymphadenopathy that is greater than 1.5 cm is one of the diagnostic criteria [16]. Bilateral non exudative conjunctivitis, often sparing the limbus, is also a classically seen symptom of Kawasaki Disease [19].

Mucocutaneous involvement, with maculopapular rash and cervical lymphadenopathy has also been reported in MIS-C [1,20] as has bilateral non-exudative conjunctivitis [19]. Studies have shown that a majority of MIS-C patients may also meet the criteria for Kawasaki Disease or atypical Kawasaki Disease [9,10]. This can obviously be one of the main reasons differentiations of the two diseases is challenging.

2.4.6. MSK/neurological/renal

Although rare, arthritis and serositis have been reported in both MIS-C and Kawasaki Disease [3,17]. A small minority of patients developed acute kidney injuries with MIS-C, and neurological complications are even less frequent although encephalopathy has been reported [17]. Reported neurological symptoms of Kawasaki Disease include sensorineural hearing loss, facial nerve palsy, severe irritability, and aseptic meningitis [3].

2.4.7. Laboratory markers

In the acute stage of Kawasaki Disease, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) are expected. Eosinophilia predominates and platelets are activated causing a reactive thrombocytosis. Decreased hemoglobin with a normocytic normochromic anemia is often an additional finding in Kawasaki Disease [21].

During the acute phase of MIS-C an elevated CRP and ESR are also expected, but leukopenia as opposed to an elevation in the WBC count. Elevated troponin, D-Dimer, and brain natriuretic peptide (BNP) are often significantly increased. Fibrinogen and ferritin levels will be elevated and often Interleukin-6 as well. Similar to Kawasaki Disease, platelets become activated, but bone marrow suppression results in thrombocytopenia [10,22].

2.5. Treatment

The primary treatment for acute Kawasaki Disease is Intravenous immunoglobulin (IVIG) and high dose aspirin [3]. IVIG should be administered within 10 days of the onset of fever to reduce risk of coronary artery lesions. If a patient is beyond the 10-day window, but continues to have fever, coronary abnormalities, or persistently elevated C-reactive protein and erythrocyte sedimentation rate, they should still be treated with standard IVIG therapy [3]. The use of IVIG within 5 days of onset of fever has been shown to significantly reduce the likelihood of coronary aneurysms [23]. Use of steroids in the treatment as first line or for refractory Kawasaki Disease has been controversial. Monoclonal antibodies such as Infliximab as well as the interleukin-1β receptor antagonist Anakinra have also been used in cases refractory to IVIG [3]. Treatment with high dose aspirin should be continued until fever has subsided [3]. If a patient has a recurrence of Kawasaki Disease or atypical Kawasaki Disease they should be treated with standard IVIG and aspirin dosing [3]. Long term management of Kawasaki Disease is beyond the scope of this review. Refer to the 2017 American Heart guidelines for more details [3].

As MIS-C is a relatively new disease, there are no standardized, well studied, evidence-based treatment protocols for MIS-C and most patients are treated based on local institutional protocols. Steroids and/or IVIG are used in patients with moderate to severe infections with high levels of inflammation and organ failure [22]. Recent studies have shown a link between expedited use of IVIG in the treatment course and decreased pediatric intensive care unit length of stay [22]. Anakinra has also been used in patients that have MIS-C refractory to steroids and IVIG or in patients where steroid use may be contraindicated [22]. Anticoagulation and anti-platelet therapies are also indicated in patients with high levels of inflammation and clotting risk factors [22].

3. Discussion

Patients with Kawasaki Disease (KD) and multisystem inflammatory syndrome in children (MIS-C) can have very similar presentations which can make it difficult to differentiate between the two diseases. The fact that most patients with MIS-C also meet criteria for Kawasaki Disease can make initial diagnosis and treatment decisions challenging. Understanding the differences in the epidemiology, diagnostic criteria, organ involvement and laboratory markers is important in guiding clinicians to distinguish between these two diseases.

Age of the patient can be helpful, with Kawasaki Disease more typically seen in younger patients and MIS-C more frequently seen in adolescents and teens. The presence of recent COVID-19 infection, exposure to confirmed COVID-19 case or positive polymerase chain reaction (PCR), serology, or antigen testing is needed to make the diagnosis of MIS-C. Coronary artery dilation or aneurysms can be found in both diseases but tend to be more common in Kawasaki Disease while elevated cardiac enzymes, ventricular dysfunction, and hemodynamic instability are more frequently associated with MIS-C. Similarly, gastrointestinal symptoms and hypercoagulability are seen more commonly in MIS-C. Elevated white blood cell count with eosinophilia and elevated platelets all point more toward the diagnosis of Kawasaki Disease while patients with MIS-C more commonly develop thrombocytopenia. Elevated D-dimer and ferritin are more common in MIS-C.

Therapies for Kawasaki Disease are well established while those for MIS-C are less well defined, less uniform and are evolving. Not surprisingly treatment for MIS-C includes many of those used in Kawasaki Disease. With ongoing clinical experience and research into MIS-C we will almost certainly gain better diagnostic tools and improved treatment options for this novel disease.

4. Conclusion

In summary, Kawasaki Disease (KD) and multisystem inflammatory

syndrome in children (MIS-C) are both auto-immune, hyper-inflammatory conditions that involve multiple organ systems. Understanding the subtle differences in clinical presentation, organ involvement and laboratory markers is important in differentiating between these two diseases.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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