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Chapter

Multisystem Inflammatory Syndrome in Children (MIS-C)

Felipe Yagnam Rojas

Abstract

The burden of disease caused by the new SARS-CoV-2 coronavirus is focused on adults. In children, this infection manifests as a mild and even asymptomatic acute respiratory illness. Reports in April 2020 described a multisystem inflammatory syndrome in children (MIS-C) occurring 2 to 6 weeks after SARS-CoV-2 wave peak. Clinical manifestations included fever, gastrointestinal symptoms, Kawasaki Disease criteria, hypercoagulability, and laboratory parameters within severe inflammatory range. There is no certainty of the pathophysiology of this syndrome. It is thought to be driven by a post-viral dysregulated immune response. The disease can be life threatening, frequently presented as rapid-onset severe organ failure and need for pediatric critical care support. Cardiovascular dysfunction and coronary involvement are the most serious complications. The clinical and laboratory features of MIS-C indicate that the inflammation is exceptionally high; thus, empirical immunomodulation is the current therapy, leading to good clinical results. Once vaccination against SARS-CoV-2 began, a drop in the incidence of MIS-C happened. In the post-COVID era, permanent vaccination of the population in countries that are already vaccinated is necessary to keep MIS-C incidence rates low. While SARS-CoV-2 is circulating in the world, MIS-C will remain as a differential diagnosis in the evaluation of sick children.

Keywords: children, COVID-19, inflammatory, pediatric, SARS-CoV-2

1. Introduction

The infection caused by the new coronavirus SARS-CoV-2 spread rapidly in the world. At the beginning of 2020, the year in which the disease was declared a pandemic by the World Health Organization (WHO) there was no certainty of its behavior in the adult population, even less how it would affect the children [1]. Time showed that COVID-19 mainly affects adults with fast-spreading lung disease, high rates of hospitalization by respiratory failure secondary to severe pneumonia, and with significant morbidity and mortality [2]. The massive need for medical care caused emergency rooms and hospitalizations around the world to collapse, yet the reality of childhood population at that time was very different. In children, COVID-19 presented as a mild and rare disease, often asymptomatic, with low need for hospitalization and low mortality [3]. Due to this opposite behavior between children and adults, a novel syndrome emerged.
adults and the collapse of health systems around the world, many pediatric services and pediatric intensive care units had to change their care and transform into adult units. These seriously ill adults were treated by staff usually dedicated to child care [4]. Many hypotheses tried to explain this phenomenon in which children were less susceptible to getting sick. No theory seemed to explain by itself the disease opposite behavior between children and adults, but the only clear thing is that infants seemed to cope very well with COVID-19. This is until April 2020, when a series of reports from the United Kingdom and Italy reported the presence of a childhood disease with a clinical presentation similar to Kawasaki Disease or Toxic Shock Syndrome, but temporarily associated with an infection by SARS-CoV-2 [5, 6]. It was a syndrome of generalized inflammation with skin and mucous membrane involvement, which could potentially seriously compromise children. The disease was soon described in the rest of Europe, America, and then around the world. It was called Multisystem Inflammatory Syndrome in children associated with COVID-19 (MIS-C) or Pediatric Inflammatory Multisystem Syndrome (PIMS). Clinical and laboratory criteria were developed to have suspicion and early diagnosis. These recommendations were initially published by WHO and the Centers of Disease Control and Prevention (CDC) and then massified by countless guidelines of pediatric scientific societies and health services throughout the world [7, 8]. The syndrome occurred with severity in a small group of children, even requiring critical care support and connection to mechanical ventilation. It was a diagnostic and therapeutic challenge for pediatric critical care teams, since the severity of these patients was determined by a multisystem compromise of uncertain behavior and not by severe pneumonia as had been seen so far in adults infected with SARS-CoV-2. We know now that MIS-C is rare and has low mortality. Although critical care is required in a small group of pediatric patients, the evolution is favorable if the diagnosis and immunomodulatory treatment is instituted in time, with complete recovery of organ involvement in most affected children [9]. The fall in the incidence of COVID-19, as well as the lower severity and decrease in mortality, was the consequence of the massive vaccination in both adults and children. This allowed the viral circulation to decrease, resulting in less SARS-CoV-2 infection in children and therefore a lower incidence of MIS-C [10]. MIS-C is rare; however, it is a differential diagnosis that should be taken into account in pediatric patients, while there is circulation of SARS-CoV-2 in the world. This diagnostic suspicion should be greater in any country with temporary peaks of infection and mainly in countries with low vaccination rates where high viral circulation can cause an increase in the presence of new variants. The SARS-CoV-2 virus is here to stay and consequently, the multisystemic inflammatory response of children to this infection is a real possibility as long as there is viral circulation.

2. Epidemiology

MIS-C is a rare complication of pediatric COVID-19. It is described in <1 percent of children with confirmed SARS-CoV-2 infection [9]. Reports from the United States describe an incidence of 2 per 100,000 infected with COVID-19 under 21 years of age [11]. Despite these reports, the incidence of MIS-C can vary significantly depending on the infectious waves as well as the susceptibility of the population that is directly related to vaccination rates [12, 13]. It mainly affects children over 5 years of age. More than 70% of affected children have no associated comorbidities [14, 15].
It is described more frequently in some races (black, Hispanic, Latino); however, there may be biases influenced by their sociocultural reality [16]. The epidemiology of MIS-C differs from adult SARS-CoV-2 infection. Although most infected children have, like adults, asymptomatic or mild respiratory symptoms, it is in the severe presentation when a difference occurs, presenting as multisystem inflammation and not as severe pneumonia. Children, massively asymptomatic, could act as a reservoir and vector of viral infection, perpetuating the circulation of the new coronavirus in adults, favoring peaks of infection in them [17]. It is these peaks that affect the incidence of MIS-C, which has a temporal association with them. MIS-C appears a few weeks after the peak of SARS-CoV2 infection. It is described between 2 and 8 weeks after the population infectious peaks, which means that MIS-C could correspond to an immune-mediated post-infectious disease. The emergence of SARS-COV2 variants has had an impact on the current occurrence of MIS-C. The Omicron wave is described as less severe in adults and with a lower incidence of MIS-C, which was reported worldwide. The Omicron waves showed that the pediatric population that was not fully vaccinated still decreased the incidence of MIS-C [18–22]. The impact of vaccination appears to influence not only the variant, but also the age at which MIS-C occurs, showing an epidemiological change with age shifting to younger children (< 5 years) who are not vaccinated [23, 24]. It is likely that this current decrease in the incidence of MIS-C is multifactorial, being related to the increasing exposure of the population to SARS-COV2, the lower viral circulation, and the massive adult and child vaccination, which probably generates variants with less possibility to create a hyperinflammation syndrome, maintaining the susceptibility of presenting the syndrome to populations with low vaccination rates.

3. Pathophysiology

MIS-C is presented late in relation to the peak of SARS-CoV-2 cases, which is why it is suggested from the outset that it would be an immune-mediated post-infectious disease. The presence of antibodies to SARS-CoV-2 often without a positive PCR made this theory more accurate. Serology is positive even up to 90% of cases; however, the molecular detection of the virus by PCR varies between 20 and 40%. Until now, the exact pathophysiology is unknown, but there are theories that try to explain how SARS-CoV-2 causes such a dysregulated response in children [25].

3.1 Immune dysregulation

SARS-CoV-2 infection in pediatric population would produce a functional activation of phagocytes and complement mediated by immunoglobulin G (IGG), similar to the response of adults with moderate COVID-19, and different to severe adult COVID-19 infection that is primarily mediated by IGA and neutrophils [26]. Once the acute infection has passed, often asymptomatic, the child persists with high levels of IGG similar to acute infection levels and with the ability to activate the immune system later. In addition, the prolonged permanence of the virus in the intestine of children is described. If intestinal inflammation is persistent, the possibility of increased permeability is real, with consequent leakage of viruses into circulation [27]. Single-cell RNA sequencing of peripheral blood mononuclear cells from children with acute MIS-C has been studied, showing low viral and bacterial
signatures, suggesting that there are no viral or bacterial infections as triggers of MIS-C [28]. The response of children to the Spike glycoprotein (S) is strong in IGG but weak in immunoglobulin M (IGM). They also have a poor immune response to the nucleocapsid protein (N) [29–31]. Adults on the other hand have a better response to protein S in any types of immunoglobulin, as well as better neutralizing capacity [32]. The asymptomatic nature of the disease in children could be related to this type of immune response. The immunoglobulin response in children with MIS-C is shown in Figure 1. Between 20 and 50% of people without exposure to SARS-CoV-2 have T cell reactivity against the virus. This may be due to some cross-reaction between CD4+ T cells and the seasonal coronavirus before the pandemic [33, 34]. Seasonal coronavirus antibodies do not vary between children with MIS-C and children hospitalized for other reasons so the role played by these previously activated T cells in the pathophysiology of MIS-C is not yet clarified [35]. High IFNy levels correlate with high levels of plasma-soluble markers from natural killer (NK) cells and T cells, suggesting that there is an increase in cytotoxic gene expression, which could contribute to tissue damage [28]. There is activation of CD8+ T cells that express inflammatory molecules of the vascular endothelium that could be related to cardiovascular alterations, D-dimer production, thrombocytopenia, and vasoactive drug requirement. This activation would be only in pediatric patients infected with SARS-CoV-2 who develop MIS-C and is related to cytotoxicity although to a less than NK. The proportion of CD8+ T cells decreases as the child’s clinical condition improves [28, 36]. Non-specific B cell activation and elevation of plasmablast can be observed [37]. Complement activation is part of the inflammatory process in MIS-C. The elevation of C5b-9 in sick patients is related to endothelial dysfunction. There is an associated within complement activation and thrombotic microangiopathy. Patients with MIS-C have a higher incidence of thrombotic events compared to healthy children or patient COVID-19 without MIS-C [38].
3.2 Superantigen theory

The virus binds to the immune cell via toll-like receptor (TLR) and is endocytosed. A fragment of SARS-CoV-2 spike glycoprotein 1 (S1) is similar to staphyloccocal enterotoxin B [39]. This viral structure interacts with a high affinity between the major histocompatibility complex II (MHC II) and CD4+ T cell receptors (TCR). This interaction between MHCII and TCR would be the same that occurs with enterotoxin B of staphylococcus, acting as a superantigen in the pathophysiology of toxic shock syndrome (TSS) [39]. An expansion of TCR β variable gene 11–2 (TRBV11–2) has been found. This TCR correlates with MIS-C severity and serum cytokine levels and it has been associated with HLA class I alleles [40]. Proteins would act as superantigen interacting not only with TCR, but also at the endothelial level between Major Histocompatibility Complex I (MHC I) and CD28+ T cells [41]. The cytokine storm that occurs in TSS occurs during acute staphylococcal infection, whereas in MIS-C SARS-CoV-2 is usually no longer detected, so the superantigen properties of SARS-CoV-2 and its role in the pathophysiology of MIS-C have yet to be confirmed.

3.3 Genetic susceptibility

All pediatric patients infected with SARS-CoV-2 have a similar antibody response, independent of whether they develop MIS-C. The fact that MIS-C only occurs in a small group of children suggests that the immune response is associated with a genetic predisposition. It is thought that there are mutations or polymorphisms of genes that encode molecules that trigger immune cascades, among other TLRs and Fcγ receptors [42]. It has been described that there could be an alteration in genes that regulate the suppression of cytokine signals (SOCS1). An alteration in these genes would mean an impossibility of stopping the inflammatory cascade in these children. Despite all the descriptions seen above, there is no specific genetic alteration that can explain why some children develop MIS-C and other does not.

3.4 Inflammatory mediators

There is an elevation of interleukin (IL) 1B, IL6, IL8, IL10, IL 17A, IFNγ, and a series of chemokines that are present in MIS-C and not in pediatric respiratory infection by COVID-19 [43, 44]. E-selectin is a molecular marker of endothelial cell inflammation and is at high levels in children with MIS-C, so endothelial involvement seems to be a contributor to the inflammatory process of all systems [28]. When measuring inflammatory markers, they differ between patients, probably by genetic susceptibility, severity of the disease, and geographic location [25]. The heterogeneity of inflammatory markers does not allow attributing the disease to a single inflammatory pathway.

In summary, MIS-C is due to a post-infectious immune dysregulation and virus-induced cytopathic effects and inflammation in multiple organ systems. Aberrant immune activation may occur by: particular variants of SARS-CoV-2; genetic predisposition (variants in the genes that encode Fcγ receptors, components of the signaling cascades, mutations in genes such as SOCS1 that regulate the immune response); SARS-CoV-2 spike protein and the formation of a superantigen; dysregulated activation of lymphocytes, with production of IGG; and complement activation and autoantibody-mediated endothelial damage (Figure 2).
Post COVID-19 - Effects on Human Health

4. Clinical manifestation

4.1 Signs and symptoms

As described above, the onset of symptoms occurs weeks after exposure to the virus. During this period, the child is usually asymptomatic. When the disease manifests clinically, it starts with general symptoms that are not very specific. Fever is present and is one of the main criteria for diagnosing the syndrome. The formation of a superantigen could amplify the inflammatory response. NK cells expand the immune response and could cause endothelial damage. The dysregulation of B lymphocytes produces autoantibodies that activate Fcγ receptors and also produce endothelial inflammation and complement activation, which contributes to increased hyperinflammation. Endothelia damaged perpetuates the inflammatory process. Endothelial dysfunction explain much of the signs and symptoms of the disease. TLR: Toll Like Receptor; MHC II: Major Histocompatibility Complex II; S protein: Spike protein; TCR: T cell receptors; MHC I: Major Histocompatibility Complex I; IL: interleukin; IFN: interferon; SOCS: suppression of cytokine signals.

Figure 2.

Theories that would explain the pathophysiology of MIS-C.
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[45, 46]. Ocular involvement can vary from 30 to 80% of cases, usually presenting as bilateral no purulent conjunctivitis. Other general symptoms may be present but in a low percentage. Neurocognitive involvement includes headache, lethargy, confusion, or irritability, which is described in less than 50% of cases [46]. Respiratory symptoms are rare during MIS-C, but may be present as a history of upper respiratory infection weeks prior to the onset of MIS-C symptoms. Lymphadenopathy is usually rare to find [47].

4.1.1 Severe presentation

So far, many children may express the disease with mild symptoms meeting the diagnostic criteria for CVC and WHO, but without cardiovascular compromise. The major problem is the group of patients who develops cardiovascular involvement. It is this involvement that reflects the severity of multisystemic inflammation and poses a potential life-threatening risk to affected pediatric population. These group of patient will need a pediatric critical care unit. It usually presents as shock, meeting most of the surviving sepsis campaign criteria, being difficult to differentiate it initially from a sepsis or a toxic shock since MIS-C usually is accompanied by cutaneous manifestations. Many children may show cardiovascular involvement due to cardiac dysfunction with or without coronary involvement. Coronary disease seems to be present more frequently than in KD. Arrhythmia is described but it is a less common presentation. Respiratory illness is rare in these critically ill patients and the need for invasive ventilatory support is often necessary for the management of pediatric shock and not for inflammation, damage or lung infection. The dysfunction of other organs is less frequent, but as it is generalized inflammatory multisystemic disease, there may be diffuse inflammation. This inflammation may present as serositis like pleurisy, pericardial effusion, and/or ascites. The liver can also be affected. There may be an increase in transaminases or even hepatitis. This condition is rare and fluctuates between 5 and 20% of cases. A neurologic clinic of mild symptoms was previously described at the beginning of symptoms; however when MIS-C is severe, it can severely compromise the central nervous system. The disease may present with encephalopathy, meningeal inflammation, and seizures [48].

4.1.2 Presentation phenotypes

The spectrum of the disease ranges from mild to severe as described above. MIS-C is new, so the factors that cause a child to evolve from mild-to-severe disease with cardiovascular involvement are still unknown. It is likely that laboratory tests that show a greater range of general inflammation are more frequently present in cases that are going to evolve to severe (3.2 laboratory tests); however, the severity of the disease is determined by cardiovascular involvement and presence of shock rather than by the results of laboratory tests [49]. What has been seen is that there are phenotypes resulting from associations combining the severity of the clinical presentation, the KD criteria, and the presence of shock. Then, we could classify the phenotype in three main forms: MIS-C phenotype KD without shock; MIS-C phenotype shock/myocarditis (with or without KD); and MIS-C phenotype without KD or shock.  

MIS-C phenotype KD without shock. This is a group of children who, regardless of age, meet the WHO or CDC criteria for MIS-C, in which the clinical presentation fully or partially fulfills the diagnostic criteria for KD. These patients may have clinical and laboratory signs of general inflammation and even organ dysfunction or
cardiac inflammation, but do not present with hypotension or signs of shock. Their laboratory tests show general and non-specific inflammation, but show no evidence of hypoperfusion.

MIS-C phenotype shock/myocarditis (with or without KD). These patients, who meet WHO and CDC criteria for MIS-C, show hypotension or evidence of shock regardless of the KD criteria. Then, we can have patients in shock with mucosal and cutaneous involvement like KD, but also patients in shock who do not show any Kawasaki signs. In them, the cardiovascular compromise can manifest as shock, by the criteria of the surviving sepsis campaign, or as myocarditis. Laboratory tests appear to show higher ranges of generic and cardiac inflammation. It is important to recognize this group of patients since they are children who require advanced monitoring and management of shock in an Intensive Care Unit (ICU).

MIS-C phenotype without KD or shock. These children also meet WHO and CDC criteria for MIS-C, but they have no clinical criteria for KD or clinical or laboratory evidence of hypoperfusion, shock or myocarditis. These patients, like the previous ones, present multisystem inflammation and organ systems involved, but without cardiovascular involvement.

All the groups have in common a generalized systemic inflammation, initiated as fever and gastrointestinal symptoms, defining their phenotypes in a few days. It is important to note that coronary alterations can be present in any of the groups. Coronary alterations are rare to observe in children, so it denotes severity of the disease, independent of filling the KD criteria and even without hypotension or shock. In summary, the clinical presentation of MIS-C can be very variable. Most children have a mild multisystem inflammatory compromise without shock; however, the recognition of cardiovascular involvement is critical. Children with Shock (with or without KD criteria) are the group of patients that will require advanced critical care support, including advanced monitoring and in some cases connection to invasive mechanical ventilation. The pediatric population with an clinical presentation of shock are the children with the highest risk of morbidity and mortality.

4.2 Laboratory test

Laboratory tests reflect children's severe inflammatory involvement. Abnormal level of blood cell counts is one of the most frequent findings. The blood count shows elevation of white blood cells of neutrophilic predominance; however, the presence of lymphopenia is described as even more frequent, up to 80–95% of cases. Moderate anemia and thrombocytopenia can be observed in many cases and can be seen in 70 to 80%. The elevation of inflammatory parameters is relevant when making the diagnosis of MIS-C and is present in the diagnostic criteria of all clinical guidelines. There is an elevation of general inflammatory parameters and also of specific cardiac parameters. The rise of C-reactive protein (CRP) into bacterial range occurs up to 90–100%. Erythrocyte sedimentation rate (ESR) is another result that is elevated up to 80%. Procalcitonin also rises up in bacterial ranges [9, 47]. Elevation of other acute phase reactants such as ferritin, dimer D, and fibrinogen also occurs in 60 to 80% of MIS-C. Hypoalbuminemia is a common finding. As stated, when signs and symptoms were described, MIS-C can present with or without shock. Patients with shock have a greater elevation of inflammatory parameters compared to children without shock, so it could be assumed that these elevated parameters are related to the severity of the disease [50, 51]. Regarding interleukins, in MIS-C there is a severe elevation of Interleukin (IL) 6. It is interesting to note that although the elevation of IL6 is severe
due to the large systemic inflammatory process that occurs in MIS-C, when compared to the IL6 measurements of pediatric septic shock, the latter are greater. This suggests that although the pathophysiological basis of MIS-C is immune-mediated, it is likely that IL6 is not the main interleukin mediating the disease [52]. Elevated cardiac inflammatory parameters seem to be important when making the diagnosis of pediatric inflammatory syndrome associated with COVID-19, since the heart is one of the main organs affected. Between 60 and 90% of patients with MIS-C can elevate troponins and/or pro BNP. As in general inflammatory parameters, cardiac laboratory elevation is greater in patients with shock than without it. The laboratory tests requested in children with MIS-C are shown in Table 1.

<table>
<thead>
<tr>
<th>Evidence of SARS-CoV-2 infection</th>
<th>Polymerase chain reaction (PCR)</th>
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<td>Serology (IGM/IGG)</td>
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<td>Inflammatory markers</td>
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<td>Erythrocyte sedimentation rate (ESR)</td>
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<td>Fibrinogen</td>
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<td>Partial thromboplastin time</td>
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<td>Cardiac inflammation</td>
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<td>Creatine kinase-MB</td>
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<td>B-type natriuretic peptide</td>
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<td>Perfusion and organ dysfunction</td>
<td>Lactate</td>
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<td>Venous and arterial gases</td>
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<td>Creatinine and Ureic Nitrogen</td>
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<td>Transaminases</td>
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<td>Other focus of infection</td>
<td>Blood cultures</td>
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<td>Urine and urine cultures</td>
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<td>Viral respiratory panel.</td>
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<td>Others according to symptoms</td>
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<td>Images</td>
<td>Chest X-ray</td>
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<td>Echocardiography</td>
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<td>Others according to sign and symptoms</td>
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Table 1. Tests required in MIS-C.
4.3 Images

There are no specific altered images in MIS-C. Chest X-ray shows no specific findings. Although infiltrates, consolidation or atelectasis may be observed, most of the patients have no acute respiratory clinic, so the most frequent finding is a normal chest X-ray. If X-ray shows pulmonary alteration, it may be a consequence of the SARS-CoV2 infection that occurred prior to MIS-C. It is rare to see a patient with an altered chest X-ray who is simultaneously in a multisystem inflammatory process, since MIS-C occurs weeks after the respiratory infection as explained above. It is possible to find pleural effusion as part of the inflammatory disease. One of the initial symptoms of the disease is abdominal pain that can even mimic an acute abdomen, so abdominal ultrasound is a study frequently requested. Like chest X-ray, abdominal images are non-specific for the disease, showing alterations that are mainly a consequence of a diffuse inflammatory process. It can observe ascites, free fluid, ileitis, and mesenteric adenopathy/adenitis. Chest or abdomen computed tomography (CT) does not show specific alterations. The most altered image study is echocardiography. There is no specific finding in cardiac ultrasound, being able to find multiple alterations alone or associated. Left ventricle (LV) dysfunction can be found up to 40% of patients with MIS-C. If the disease presents clinically as shock, depression of LV function is more frequent, being present in up to 60% of these severe cases. Heart valve diseases such as mitral or tricuspid regurgitation also may be found. Pericardial effusion can be seen, and as well as pleural effusion and ascites, it is due to a generalized inflammatory process with serositis. One of the most important findings of the disease is the alteration of the coronary arteries (CA). This type of alteration is very rare in children, with KD being one of the few pediatric diseases in which it is present. CA abnormalities include dilation or aneurysm. This alteration may be present up to 25% of mild cases and even up to 50% in severe cases with shock. CA assessment is based on Z-scores used in KD [53–55]. Performing cardiac nuclear magnetic resonance imaging (MRI) is rare, but when it has been done, myocardial edema and abnormal strain is described, compatible with a generalized cardiac inflammatory process [56].

5. Diagnosis

5.1 Case definition

The CDC or WHO criteria are the most commonly used case definition. Regardless of the institution that defines the case, all definitions have some pillars to make the diagnosis. The first is a pediatric patient with fever. The second is to have inflammation of at least two systems, by clinical presentation or by laboratory test. The third is to have altered laboratory parameters that show a systemic and generalized process of inflammation. The fourth is to have ruled out any infection that is not COVID and finally any epidemiological association with SARS-CoV2 infection [7, 8]. Case definition criteria are shown in Tables 2 and 3.

The criteria can be modified over time as there is more knowledge of the syndrome. CDC will change the current case definition in 2023. Among main changes are fever lasting >24 hrs. Will be changed by subjective or documented fever >38.0°C. Illness requiring hospitalization will be changed for severe illness that requires hospitalization.
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1 Age 0 to 19 years
2 Fever for ≥ 3 days
3 Clinical signs of multisystem involvement (at least 2 of the following):
   • Rash, bilateral no purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
   • Hypotension or shock
   • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities
   (including echocardiographic findings or elevated troponin/BNP)
   • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
   • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4 Elevated markers of inflammation (e.g., ESR, CRP, or procalcitonin)
5 No other obvious microbial cause of inflammation.
   (including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes)
6 Evidence of SARS-CoV-2 infection (any of the following):
   • Positive SARS-CoV-2 RT-PCR
   • Positive serology
   • Positive antigen test
   • Contact with an individual with COVID-19

World Health Organization [7].

Table 2.
WHO MIS-C case definition (all criteria are required).

1 Fever >38.0°C or subjective fever lasting >24 hrs.
2 Illness requiring hospitalization
3 Laboratory evidence of inflammation (e.g., CRP, ESR)
4 Multisystem organ involvement (at least 2 of the following):
   • Cardiac (e.g., shock, Troponin elevation, BNP elevation, abnormal echo, arrhythmia)
   • Dermatologic (e.g., rash, mucocutaneous lesions)
   • Gastrointestinal (e.g., diarrhea, bilirubin or liver enzyme elevation)
   • Hematologic (e.g., D-dimer elevation, thrombophilia, thrombocytopenia)
   • Neurologic, Renal, Respiratory.
3 Positive for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset symptoms.

Health Alert Network (HAN) [8].
CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, BNP: B-type natriuretic peptide, and PCR: polymerase chain reaction.

Table 3.
2020 CDC MIS-C case definition (all criteria are required).
and may result in death. Laboratory makers of inflammation will be limited to just CRP > 3 mg/dl. Shock will appear as a separate criterion of cardiac involvement. Coronary involvement will include coronary dilatation/aneurysm and left ventricular ejection <55%. Dermatological criteria will be more explicit: oral mucosal inflammation, conjunctivitis/conjunctival injection, or extremity findings (erythema, edema). Gastrointestinal criteria will be limited to abdominal pain, vomiting, or diarrhea. Renal, respiratory, and neurologic organ system involvement will be removed.

5.2 Differential diagnosis

Because it is a disease that can have many clinical presentations, there are many possible differential diagnoses but there are some of them that are essential to rule out. In many cases, the disease simulates sepsis or septic shock, both by its clinical presentation or by laboratory tests in ranges that simulate bacterial infection. The main difference is that in MIS-C there is no bacterial infectious focus and that no infectious agent is isolated. The association with SARS-CoV-2 as the only infectious agent it is absolutely necessary.

5.2.1 Infectious inflammatory diseases

Appendicitis: MIS-C may present as acute abdomen. Fever added to abdominal pain and tests in bacterial range make appendicitis difficult to rule it out. At the beginning of the pandemic, cases of children undergoing laparoscopies for suspected appendicitis were reported in which normal appendices were found. To dismiss the diagnosis of appendicitis, an abdominal image (ultrasound or CT) is required. In MIS-C, this image shows non-specific abdominal inflammatory findings but no inflammation of the cecal appendage.

Sepsis y Septic Shock: It is one of the main diagnoses to discard. Aforesaid, MIS-C simulates a bacterial infection, with fever and laboratory parameters in bacterial range, even in severe cases of MIS-C may show evidence of shock. That is why many established protocols suggest the initiation of antibiotics empirically and then suspend them once an infectious focus has been ruled out. Unlike septic shock, MIS-C does not have a specific infectious focus and bacterial infectious agents cannot be identified. It is necessary to take cultures to rule out the main bacterial pediatric infectious diseases. At least blood cultures are required to rule out bacteremia and complete urine with urine culture to rule out urinary focus. Other studies may be added depending on the clinical presentation. Intestinal pathogens can be searched if gastrointestinal clinic predominates. Study of cerebrospinal fluid can be studied if the predominant clinic is neurologic. Other studies depend on each case. With negative cultures and once any clinical focus is dismissed, the bacterial cause of the inflammatory process should be ruled out.

Toxic Shock Syndrome (TSS): It has many similarities with MIS-C, since they share the multisystem inflammation, laboratory tests in similarly high ranges and the skin involvement. The main difference between both conditions is the presence of a clinical focus and the bacterial origin of the (TSS). Cultures are required to determine staphylococcal or streptococcal infection.

Other viral infections: There are viral pathogens that can cause systemic inflammation and skin involvement, including this adenovirus, cytomegalovirus, Epstein Barr virus, enterovirus, and parvovirus among others. Infection with these agents often occurs in immunosuppressed patients. In general, these viral infections do not produce an elevation of inflammatory parameters in bacterial range. If the suspicion
exists, molecular study by polymerase chain reaction is necessary to confirm the presence of this viral infection.

5.2.2 Immune-mediated inflammatory diseases

Kawasaki disease: This is a challenge as they share a large number of clinical and laboratory elements. The situation becomes more difficult if the MIS-C does not meet all the KD criteria, with the incomplete Kawasaki being more difficult to distinguish from a MIS-C. The keys to differentiate them could be the gastrointestinal symptoms that are more frequent in MIS-C, cardiovascular dysfunction, and shock that are rare in KD (KD shock syndrome has an incidence rate of only 3.3–7% of KD cases) [57], high inflammatory parameters in laboratory tests associated with lymphopenia most common in MIS-C and the temporal association or evidence of exposure to SARS-CoV-2 [25].

Systemic lupus erythematosus (SLE): Like MIS-C, SLE is a multisystem immune process which can have skin involvement and that occurs with elevation of inflammatory parameters often in bacterial ranges. One of the elements to be taken into consideration to differentiate these diseases is age, being SLE more frequent in adolescent patients; female sex that is predominant in SLE, renal involvement that is much less frequent in MIS-C; and the neurological compromise that is most associated with SLE.

Hemophagocytic lymphohistiocytosis (HLH): Macrophage activation syndrome (MAS). This disease shares characteristics with MIS-C, both in multiorgan involvement and in laboratory parameters. It usually occurs in patients with a history of immune-rheumatologic diseases, but can also be triggered by viral or bacterial infectious diseases in previously healthy patients. There are diagnostic criteria published by the histiocyte society. Fever, high C-reactive protein, high ferritin, and thrombocytopenia are elements that it shares with MIS-C; however, the compromise of other lines of the blood count as well as the increase in triglycerides is not common in MIS-C. One of the most important tests for HLH/MAS is the elevation of soluble CD25, which does not occur in MIS-C.

6. Treatment

Treatment has two goals. The first is to stop hyperinflammation and the second is to treat cardiovascular complications that could be associated in severe cases. At the time of this publication, there are no randomized controlled studies evaluating the treatment of MIS-C.

6.1 Treatment of hyperinflammation

Many ways to immunomodulate the disease are described, most of them initially borrowed from Kawasaki disease and other hyperinflammatory syndromes. They could be grouped into three approaches: the use of intravenous immunoglobulin (IVIG), the use of steroids, and the use of biological drugs.

6.1.1 IVIG and steroids

VIG is the most commonly used drug to modulate MIS-C followed by glucocorticoids. There are few comparative studies between the use of IVIG and steroids, and
their results are contradictory. On the one hand, some studies would suggest that the joint use of both therapies appears to have some impact on signs or symptoms, as well as in severe cardiovascular evolution (v/s IVIG alone). On the other hand, some publications suggest that patients who meet the WHO criteria for MIS-C are treated with glucocorticoids and they would have a possible benefit (v/s IVIG alone). Moreover, other studies show no difference between using IVIG alone, steroids alone, or the two therapies together. In view of the lack of evidence, but with the clarity that patients respond to immunomodulatory therapy, scientific societies have published treatment recommendations. American College of Rheumatology (ACR) recommends the use of IVIG as a first line in all patients with MIS-C with addition of glucocorticoids in the presence of shock, organ-threatening disease or refractory disease. There are countless protocols, adapted according to each local reality. The recommended doses of IVIG are 2gr/kg/day once. Methylprednisolone doses vary according to protocols between 2 and 10 mg/k/day for 3 days. In general, patients respond to the use of IVIG and steroids. Patients who maintain fever and elevated inflammatory parameters are considered refractory. In this type of patients, the use of biological drugs is considered [58].

6.1.2 Biological drugs

The use of biological therapy as rescue in patients refractory to IVIG/steroid treatment is described in many protocols. Like other therapies, these drugs were extrapolated from the treatment of KD and other diseases with systemic inflammatory processes. In order to block the effect of IL-1B, anakinra (an IL-1 receptor blocker) has been used. Another IL receptor blockade described is IL-6 by tocilizumab. Infliximab is another monoclonal antibody, used in refractory KD, to stop the effect of tumor necrosis factor alpha (TNFa) [59]. This drug is also described as a therapeutic tool in refractory MIS-C. As shown in Figure 2, the pathophysiology of MIS-C is complex. Trying to stop an inflammatory cascade by blocking a single pathway seems unlikely. IL6 is elevated in both MIS-C and pediatric septic patients (both diseases with immune dysregulation). Septic patients have higher IL-6 plasmatic levels and have good outcomes without using interleukin blockade, suggesting that there is no clear role of some IL6 in the pathophysiology of MIS-C [52]. The use of biological drugs is continuously studied for this pathology.

6.2 Treatment of cardiovascular complications

Severe MIS-C can lead to severe cardiovascular dysfunction that can be life threatening for children. Endothelial involvement and cardiac dysfunction (with or without coronary alteration) can lead to hypotension, hypoperfusion, and dysfunction of other organs. It must be managed as shock, and in many cases it requires volume, vasoactive drugs, and even connection to mechanical ventilation as part of shock management. Due to the compromise of vascular tone, norepinephrine is indicated. If there is cardiac dysfunction, epinephrine should be associated. In the case of coronary alterations, anti-inflammatory and antiplatelet treatment with acetylsalicylic acid is used in MIS-C protocols. This management was extrapolated from KD protocols. Although abnormal coagulation parameters are frequently reported, thrombotic or embolic events were rare, in contrast to adult COVID-19 [59, 60]. Other management of vascular complications includes the possibility of thrombosis. High D-dimer is frequently found in this disease and could be associated with greater hypercoagulability,
which is why many protocols include the use of anticoagulation such as enoxaparin until the inflammatory process and D-dimer go down.

7. Prognosis

MIS-C can be potentially life threatening. The need for admission to ICU was described, 40% of patients needs inotropic drugs, 15% is connected to mechanical ventilation, and even needs for extracorporeal oxygenation membrane (ECMO) have been reported. Despite what has been described, MIS-C is a disease with low mortality, less than 2%. Recovery from acute organ dysfunctions occurs quickly with a median ICU length of stay of 5 days. Recovery from sequelae is close to 6 months; however, there are reports of poor exercise tolerance. The disease was found less than 3 years ago, so large follow-up studies of these patients are needed to determine the long-term outcomes of these children [61].

8. Prevention

Early recognition of the disease is fundamental through the signs and symptoms described, in order to perform a precocious immunomodulatory treatment that allows the control of the disease and better outcomes. Clinical alert should be maintained as long as SARS-CoV-2 is circulating within the population. While clinics maintain the search for MIS-C in febrile children, it is necessary at the same time preventing waves of new viral variants and the emergence of high rates of MIS-C which until now remains low. It seems that the only way to prevent the disease is to maintain vaccination of the entire population. SARS-CoV-2 is a virus that is here to stay, but can be controlled by vaccination. The massive inoculation of the population led the virus to mutate into variants that are apparently less susceptible to producing severe inflammatory phenomena in children, as seen in the omicron wave. If the world population lowers its vaccination rates, it is likely that the virus will continue to mutate, giving the possibility of new variants that could have the potential to cause higher MIS-C rates again. It is possible that areas with less economic development and therefore less access to vaccines keep low vaccination rates. In those places, the possibility of the appearance of new variants could be high. Efforts should also be maintained for the implementation of the vaccine at all pediatric ages, given the actual change in the epidemiology of MIS-C at younger ages without access to vaccination.

9. Conclusion

MIS-C is a newly emerging disease that shares its clinical presentation simulating other serious pediatric diseases, which implies a diagnostic challenge for clinicians. Its pathophysiology is not well known but it is clear that it is a post-infectious immune syndrome. Life threatening is given by cardiac and vascular involvement. In the post-COVID era, the effort must then focus on maintaining the clinical search for the disease, maintaining vaccination of both adults and children, and in prioritizing less developed countries with poor access to vaccination.
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