ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

COVID-19-associated Multisystem Inflammatory Syndrome: a pediatric complication during the pandemic

Síndrome Inflamatória Multissistêmica associada à COVID-19: uma complicação pediátrica da pandemia

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ABSTRACT

Since the emergence of the COVID-19 pandemic, cases of late fever and systemic inflammation similar to Kawasaki Disease have appeared in the pediatric population, this entity was called Multisystem Inflammatory Syndrome associated with COVID-19. The presentation can range from just prolonged fever to severe gastrointestinal and cardiac involvement with refractory shock and multiple organ failure. Carotid aneurysms can arise in the course leading to long-term complications. The prompt recognition of this syndrome with early treatment with general support, use of Human Intravenous Immunoglobulin and other immunomodulatory drugs, can prevent progression to severe and even fatal cases, as well protect the patient from chronic complications, especially the cardiac ones.

Keywords: Systemic inflammatory response syndrome, Coronavirus infections, mucocutaneous lymph node syndrome.

RESUMO

Desde o surgimento da pandemia de COVID-19, casos de febre e inflamação sistêmica tardias, similares à Doença de Kawasaki, têm surgido na população pediátrica, sendo denominados Síndrome Inflamatória Multissistêmica associada à COVID-19. Estes quadros podem ir de apenas febre prolongada, até grave envolvimento gastrointestinal e cardíaco, com choque refratário e falência de múltiplos órgãos. Aneurismas de carótida podem surgir na evolução, levando a complicações em longo prazo. O pronto reconhecimento desta entidade com tratamento precoce de suporte geral, uso de imunoglobulina humana endovenosa e outras drogas imunomoduladoras, pode evitar evolução para casos graves e até mesmo fatais, assim como proteger o paciente de complicações crônicas, principalmente cardíacas.

Descritores: Síndrome de resposta inflamatória sistêmica, infecções por Coronavirus, síndrome de linfonodos mucocutâneos.

Introduction

Since the emergence of the Coronavirus pandemic in 2019, we have noticed that children and adolescents have been less affected. National statistics from Asia, Europe, and North America show that pediatric cases are about 2.1% to 7.8% of total COVID-19 cases.[1-3] And in those infected individuals, symptoms are milder in children than in adults, with a small proportion of children requiring hospitalization.[4] However, with the evolution of the pandemic, cases of febrile conditions began to be reported about 4-6 weeks after peaks of acute infections caused by SARS-CoV-2.[5] A study by the Centers for Disease Control and Prevention (CDC) documented the presence of 570 cases and 10 deaths, with a mean age of 8.3 years, and 99% of the cases had RT-PCR or positive serology for COVID-19.[6]

The clinical presentation is similar to other multisystem inflammatory conditions known in Pediatrics, such as Kawasaki Disease and Toxic Shock Syndrome,[7,8] but this new entity has some peculiarities, which is called "COVID-19 Multisystemic

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Inflammatory Syndrome (MIS-C)". The main symptoms are: prolonged fever, diarrhea, skin rash, conjunctivitis, edema of the extremities, mucosal changes, involvement of the central nervous system, cardiac lesions and coronary artery aneurysms, which may progress to cardiogenic shock and multiple organ failure.[9]

Unlike Kawasaki disease, which preferentially affects the Asian population and those under 5 years old, MIS-C occurs in older individuals (cases described even in patients aged 21 years old) and is more prevalent in African-American and Hispanic population.[10] Other more striking features of MIS-C in relation to other inflammatory syndromes are that abdominal symptoms, leukopenia, elevation of brain natriuretic peptide (BNP), troponin, CRP and ferritin are much more prominent.[11]

Pathophysiology

The pediatric population has a lower tendency to present severe acute cases of COVID-19, probably due to molecular alterations existing in adults and children. The primary receptor for virus entry into cells is the angiotensin-2 converting enzyme (ACE2). ACE2 is co-expressed in association with a transmembrane serine protease (TMPRSS2), which is responsible for cleaving the viral spike protein into two fragments: S1, essential for viral attachment; and S2, which guides viral fusion into the target cell.[12] Children express a lower amount of ACE2 in their pulmonary epithelium, and the expression of TMPRSS2 is regulated by levels of androgens and their receptors, which are reduced in children under 12 years of age.[13]

The emergence of MIS-C may be associated with a mechanism called antibody-dependent enhancement. It has been described in other viral infections such as dengue and Zika virus.[14] It consists of the formation of immune complexes containing the viral antigen and non-neutralizing antibodies. The FC portions of these non-neutralizing immune complex antibodies bind to specific receptors on immune cell membranes, leading to virus entry into the cell in a manner independent of traditional viral spike protein binding to ACE2. Non-neutralizing anti-spike antibodies to SARS-CoV-1 have been implicated in the worsening of inflammation in primates and in human macrophages, which leads to the hypothesis that this same type of antibodies against SARS-CoV-2 may be associated with the exacerbated inflammatory response of MIS- C.[15]

The innate immune system appears to be responsible for the inflammatory cascade that leads to tissue damage. Macrophages, stimulated by the antibody response, increase viral uptake, leading to increased production of pro-inflammatory cytokines, in a phenomenon called cytokine storm.[16] Sera from patients with MIS-C reveal elevated levels of IL-1B, IL-6, IL-8, IL-10, IL-17, interferon gamma and TNF.[5]

Immunophenotyping by flow cytometry shows B and T cell lymphopenia, with reduced CD4, CD8, gd cells.[17]

Autoantibodies have also been implicated in the pathogenesis of MIS-C. Anti-endoglin, anti-MAP2K2 (mitogen-activated protein kinase 2), anti-casein kinase, anti-Jo and anti-La antibodies were detected, as well as antibody reactivity against proteins involved in immune regulation, endothelial function and gastrointestinal biology. The generation of autoantibodies is very interesting in trying to explain part of the exaggerated immune response, but its exact role in the pathogenesis of MIS-C has not yet been determined.[5]

Neutrophils also play their role, with the formation of extracellular neutrophil traps (NET). These act as a network of free DNA, histones and neutrophil granule content, amplifying the inflammatory response and generating a prothrombotic state.[18]

Clinical condition

The case definition of MIS-C is based on the clinical presentation: evidence of involvement of two or more organs, absence of other evident infectious causes, and confirmation of infection or recent exposure to SARS-CoV-2.

The clinical spectrum ranges from a persistent febrile condition, through a situation that simulates Kawasaki Disease, to severe conditions with refractory shock and multiple organ failure.[19]

The World Health Organization criteria for the diagnosis of MIS-C are listed below.

(1) Age: 0-19 years.

(2) Signs of inflammation: fever and elevation of inflammatory markers (CRP, ferritin) for three or more days.

(3) Main features (at least two of the following items):

– bilateral non-purulent conjunctivitis or mucocutaneous rash;
– shock or hypotension;
– myocardial dysfunction, pericarditis, valvulitis or changes in coronary arteries (includes echocardiographic findings, elevation of troponin or BNP);
– evidence of coagulopathy (altered prothrombin time, KPTT, D-dimer elevation);
– acute gastrointestinal disorders (diarrhoea, vomiting, abdominal pain).

(4) Exclusion of other infectious causes.

(5) RT-PCR or COVID-19 positive serology, or recent (4 weeks) contact with patients with COVID-19.[19]

Compared to Kawasaki Disease, a greater number of patients with MIS-C present with cardiac involvement, gastrointestinal symptoms, hyponatremia, hypoalbuminemia. About 80% of patients with MIS-C have cardiac lesions, with elevated levels of troponin and BNP.[20]

Treatment

There is still no unified treatment protocol for MIS-C, but most reference centers have adopted specific protocols, based on the treatment of Kawasaki Disease, always involving a multidisciplinary team with a pediatrician, intensive care specialist, infectious disease specialist, cardiologist and immunologist.

General support is crucial, with attention to vital signs, hydration and metabolic status. Vasoactive drugs may be needed, and treatment with broad-spectrum antibiotics is recommended.

The first specific treatment option is the use of intravenous human immunoglobulin, at a dose of 2 g/kg, infused slowly for about 12 hours. Other immunomodulating drugs, such as Infliximab (anti-TNF), Tocilizumab (anti-IL-6) and Anakinra (anti-IL-1R) have shown levels of efficacy, however there is no consensus on their use, and they can be applied according to the availability and experience of using the service team.[21]

The use of steroids is recommended. Low-dose dexamethasone appears to be beneficial in suppressing the exaggerated immune response. Other drugs, such as methylprednisolone and prednisolone, have also been used, but further studies are needed to identify the true role of steroids, their optimal doses and which specific drug is most appropriate.

Assessment of coagulopathy is imperative, and if there are changes in D-dimer levels or in the coagulogram, anticoagulant therapy should be discussed with a pediatric hematologist. Low-dose aspirin (3-5 mg/kg) is used until the echocardiographic assessment excludes the presence of lesions or aneurysms in the coronary arteries.[22]

Coronary aneurysms have been identified not only in severe cases, but also in cases where the only manifestations were fever and changes in inflammatory markers. Therefore, the echocardiographic assessment and dosage of troponin and/or BNP in the initial approach is mandatory. In severe cases, follow-up with daily echocardiograms may be necessary, as well as performing this exam at the time of discharge and two and six weeks after discharge.[23] Cardiac magnetic resonance imaging can be used, but it is an exam restricted to large centers and is difficult to perform, especially in young patients and in a severe general condition.[24]

The patient can be discharged from the hospital when he is afebrile, normotensive, hydrated, without the need for supplemental O_2, and whenever the evidence of inflammatory activity is normal.

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