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The COVID pandemic in children: an alert

La pandemia de COVID en niños: una alerta

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Palabras clave:
Síndrome inflamatorio multisistémico en niños asociado con COVID-19, MIS-C PIMS-TS, síndrome inflamatorio multisistémico tipo Kawasaki.

ABSTRACT

During the initial months of the COVID-19 pandemic, the disease was thought to be benign and infrequent in children. Since March, multisystem inflammatory syndrome (MIS-C) in children associated with the pandemic has emerged as a serious disease. It has similarities with Kawasaki disease, but also important differences, such as older age, additional abdominal symptoms, respiratory difficulties, increased severity of inflammation, heart failure, and shock. We speculate in this review: 1. If MIS-C is an accelerated form of Kawasaki disease. 2. If it is a different form. 3. Simply MIS-C is a serious variant of COVID 19 in children. The presence of the multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C or PIMS-TS), in much of the world, should alert the medical community in countries where it has not yet been recognized.

RESUMEN

Durante los meses iniciales de la pandemia de COVID-19, se pensaba que la enfermedad en los niños era benigna y poco frecuente, a partir de marzo ha surgido el síndrome inflamatorio multisistémico (MIS-C) en niños asociado con la pandemia como una enfermedad grave. Tiene similitudes con la enfermedad de Kawasaki, aunque también importantes diferencias, como mayor edad, adicionales síntomas abdominales, escasos respiratorios, incremento en la severidad de la inflamación, falla cardiaca y choque. Especulamos en esta revisión: 1) si MIS-C es una acelerada forma de Kawasaki, 2) si se trata de una entidad diferente, o 3) simplemente MIS-C es una variante grave de COVID-19 en niños. La presencia del síndrome inflamatorio multisistémico en niños asociado con COVID-19 (MIS-C o PIMS-TS), en buena parte del mundo, debe alertar a la comunidad médica en los países en los que por el momento no se ha reconocido.

INTRODUCTION

The incidence of COVID-19 infection in the pediatric population during the initial months of the pandemic was very low. It was found in 1-5% of all confirmed cases in a systematic review of 45 published works,[1] with a course that was almost always benign, only two children died by March 20, so the attention was focused mainly on adults with comorbidities.[2-6] The relationship of MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves post-infectious immune dysregulation. Patients with MIS-C should ideally be managed in a pediatric intensive care environment since rapid clinical deterioration may occur. Objectives: to describe the characteristics of children and adolescents affected by an outbreak of Kawasaki-like multisystem inflammatory syndrome and to evaluate a potential temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and compare these characteristics with other pediatric inflammatory disorders.

However, as of March, a group of doctors in England observed cases in school children with a clinical picture ranging from fever, rash, conjunctivitis, gastrointestinal symptoms, shock, multiple organ failure with indicators of cytokine storm and cardiac biomarkers.[7] The alert was issued by the National Health Service of the United Kingdom, the Royal College of Pediatrics World Health Organization, the European Center for Disease Prevention Centers for Disease Control and Prevention of the United States.[8] The name assigned to

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this condition in Europe is Pediatric Inflammatory Multisystem Syndrome associated with SARS-CoV-2 (PIMS-TS). While in America it is called multisystem inflammatory syndrome in children (MIS-C). The English group reported 58 hospitalized cases. Interestingly 78% had positive evidence for SARS-CoV-2 by IgG. All children had indicators of inflammation and similar difficulties with Kawasaki disease, including but not limited to the development of coronary abnormalities in 14%.[7] Since then publications on this syndrome have appeared in Italy,[9] Spain,[10] Switzerland,[11] and France,[12,13] reporting at least 70 cases. The French group studied 21 children with clinical signs and symptoms similar to that observed by the English group but with a higher proportion of positivity to SARS-CoV-2 and myocarditis. The similarities with Kawasaki disease were notable to the extent that they coined in their work the term Kawasaki-like multisystem inflammatory syndrome in children. They also found, like other groups, differences with this disease: older age (mean 7.9 years), (in Kawasaki 80% are younger than 5 years[14]) more abdominal symptoms, myocarditis, higher elevations of inflammatory markers, (procalcitonin X10 times higher compared to the measurement in patients with Kawasaki and shock). Additionally, African ancestry was identified in the majority of Paris patients.[13] In contrast, Kawasaki disease, although known in most countries, including Mexico, is much more frequent in children of Japanese descent.[14]

Several publications have appeared in North America.[15-18] The New York series had 33 cases and an average age of 10 years, Hispanic or Latino descent was 66% of the cases. The levels of C-reactive protein, procalcitonin, d-dimer, and pro-BNP were elevated in all patients. Left ventricular ejection fraction (LVEF) was found to decreased in 66% of the cases. In this series, only one patient died (3%).[18]

Most children with MIS-C have been treated with IV immunoglobulin, and aspirin (as in Kawasaki disease). Additionally, several have received high doses of steroids. Only in a few cases, tocilizumab was used. Around 50% have required intensive therapy while a few have needed extracorporeal membrane oxygenation (ECMO). The response to treatment has been favorable in most cases.[9-13,15-18]

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QUESTIONS AND HYPOTHESES

1. The relationship of MIS-C or PIMS-TS with SARS-CoV-2 is currently only temporary. Up to date, there is no causality evidence. The suggested hypothesis proposes that it is a delayed hyperimmune reaction to infection with SARS-CoV-2. This delay can be supported by the cases of children negative to PCR but positive to IgG. It could also explain what happened in the New York cases: its appearance was observed one month after the peak in adults. However, several questions arise: Why have no cases been described in China? It could be a higher susceptibility in western populations or due to a possible mutation of the virus. The link to COVID-19 with the new syndrome would be strengthened if, in the countries where the pandemic has been reduced, the incidence of MIS-C cases also decreases.
2. What is the relationship between MIS-C or PIMS-TS to Kawasaki disease?
   A surprising fact in this relationship is the Lombardy report in Italy. The region most affected by the pandemic reported a 30 times higher incidence of Kawasaki cases when compared to the average incidence of the previous five years.[9]
   Kawasaki disease is the leading cause of acquired heart disease in children.[19] An entity that has been known for more than 50 years due to an unknown etiology, widely dispersed throughout the world. It has been associated with previous respiratory virus infections, but not all have this history. Children present an inflammatory disease with medium-caliber vasculitis with a predilection for coronary arteries where aneurysm formation is the most feared complication.[20] While MISC-C patients are older, less coronary disease, but cardiac dysfunction and shock are more frequent. In Kawasaki, IL-1 elevation plays an important role.[21] By contrast, in MIS-C, IL-1 is normal with an elevated level of IL-6. We can now make the following speculations: 1. MIS-C is an accelerated Kawasaki, 2. It is a different

entity, or 3. simply MIS-C is a serious variant of COVID-19 in children. In any case, it is difficult to avoid a relationship with SARS-CoV-2. More in-depth studies will be necessary to clarify these doubts. Recently, the WHO has made a website available to register new cases of MIS-C from anywhere in the world. In America, Texas Children's Hospital, and Baylor College of Medicine in Houston with SISIAC, also have a website: https://tch-redcap.texaschildrens.org/REDCap/surveys/?s=M3C98E7KYJ to register new cases.[22]

THE SITUATION IN LATIN AMERICA

In Mexico, more than 500 cases of Kawasaki were reported annually during the last 5 years[23] and coronary complications are well known.[24,25]

Up to date, we have not found any reported case of MIS-C or PIMS-TS, in Latin America. However, it could be possible that with the increasing number of cases in this region of the world, new cases will appear with this new syndrome.

CONCLUSIONS

COVID-19-associated multisystem inflammatory syndrome in children (MIS-C or PIMS-TS) has emerged as a serious disease temporarily related to COVID-19. It has similarities to Kawasaki disease, but also important differences, such as older age, more abdominal symptoms, respiratory difficulties, more severe inflammation, heart failure, and shock. IL-6 is significantly elevated while IL-1 is normal. The suggested pathophysiology proposes a delayed hyperimmune reaction to infection with SARS-CoV-2. Timely cared patients have responded well to treatment with IgG, aspirin, and steroids, as do Kawasaki patients. We speculate in this review if MIS-C is an accelerated Kawasaki disease, a different entity, or a serious variant of COVID-19 in children.

Further studies are needed to answer these questions. In any case, the wide spreading of COVID-19 associated with multisystem inflammatory syndrome in children (MIS-C) should alert physicians in countries where this syndrome has not been observed so far.

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