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Multisystem Inflammatory Syndrome in Children in Western Countries? Decreasing Incidence as the Pandemic Progresses?

An Observational Multicenter International Cross-sectional Study

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Background: SARS-CoV-2 variations as well as immune protection after previous infections and/or vaccination may have altered the incidence of multisystemic inflammatory syndrome in children (MIS-C). We aimed to report an international time-series analysis of the incidence of MIS-C to determine if there was a shift in the regions or countries included into the study.

Methods: This is a multicenter, international, cross-sectional study. We collected the MIS-C incidence from the participant regions and countries for the period July 2020 to November 2021. We assessed the ratio between MIS-C cases and COVID-19 pediatric cases in children <18 years diagnosed 4 weeks earlier (average time for the temporal association observed in this disease) for the study period. We performed a binomial regression analysis for 8 participating sites [Bogotá (Colombia), Chile, Costa Rica, Lazio (Italy), Mexico DF, Panama, The Netherlands and Catalonia (Spain)].

Results: We included 904 cases of MIS-C, among a reference population of 17,906,432 children. We estimated a global significant decrease trend ratio in MIS-C cases/COVID-19 diagnosed cases in the previous month ($P < 0.001$). When analyzing separately each of the sites, Chile and The Netherlands maintained a significant decrease trend ($P < 0.001$), but this ratio was not statistically significant for the rest of sites.

Conclusions: To our knowledge, this is the first international study describing a global reduction in the trend of the MIS-C incidence during the pandemic. COVID-19 vaccination and other factors possibly linked to the virus itself and/or community transmission may have played a role in preventing new MIS-C cases.

Key Words: COVID-19, multisystemic inflammatory syndrome in children, children, incidence, epidemiology

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Multisystemic inflammatory syndrome temporally associated with SARS-CoV-2 infection in children (MIS-C) has been reported worldwide.[1–7] The case definition of MIS-C has been established by different institutions and organizations such as the US Centers for Disease Control and Prevention (CDC) (May 14, 2020),[8] the Royal College of Paediatrics and Child Health in the United Kingdom (RCPCH) (May 1, 2020)[9,10] and the World Health Organization (WHO) (May 15, 2020).[11] Best practice recommendations for the diagnosis and management of children with MIS-C have been published by different research groups, some of them including data from low- and middle-income countries.[12,13] Other publications have focused their research on risk factors, immune biomarkers, outcomes of MIS-C cases and even its relationship with Kawasaki disease.[14–17]

It is difficult to estimate the real incidence of MIS-C per every child infected with SARS-CoV-2, because during acute

infection these individuals are often asymptomatic and therefore may not get tested.[18,19] The highest incidence of MIS-C usually follows peaks of COVID-19 infections by a median of 4 weeks (range 2–5 weeks).[6] Most reports estimate the MIS-C incidence is between 30 and 45 per 100,000 children and young adult population infected with SARS-CoV-2.[20,21]

In addition, MIS-C incidence has changed through the course of the pandemic. Shifting incidence rates can be a result of more of the population being immune, as a result of vaccination or previous infection. Also, new SARS-CoV-2 variants may have differential effects on the inflammatory response in children.

In this study, our aim was to report a time-series analysis of MIS-C incidence in different countries or geographical areas. We determined if there was a decline, stabilization or elevation of MIS-C cases temporal trend over time. Also, the differences between countries were analyzed. For this purpose, we collected all the MIS-C cases and COVID-19 pediatric diagnosis data from a wide range of countries from the north and south hemispheres between June 2020 and November 2021.

METHODOLOGY

Study Period and Sites

This is a multicenter, international observational cross-sectional study. Our aim was to report a time-series analysis of the incidence of MIS-C in children under 18 years for different countries or geographical areas between July 2020 and November 2021. The participating sites are Chile, Colombia (Bogotá-HOMI, Fundación Hospital Pediátrico la Misericordia), Costa Rica, Lazio (Italy), Mexico (District Federal), The Netherlands (nation-wide registry www.covidkids.nl), Panamá and Catalonia (Spain) (community-wide registry, www.copedicat.cat) (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E816). To avoid any potential selection bias regarding COVID-19 diagnosis, we did not include the MIS-C cases diagnosed before July 2020 because the diagnostic effort to detect SARS-CoV-2 infections was very scarce worldwide at that moment due to the lack of available diagnostic tests.

Data Sources

MIS-C cases were reported by the participant researchers. For Chile, The Netherlands, Costa Rica and Catalonia (Spain), the researchers compiled all the MIS-C cases for the whole region or country. For Lazio (Italy), Mexico DF, Panama and Bogotá (Colombia), we included the MIS-C cases diagnosed at a pediatric referral hospital for these sites. Data sources for each of the sites are specified in Table, Supplemental Digital Content 2, http://links.lww.com/INF/E816. In most of the sites, it was possible to split the cases per age ranges.

Regarding COVID-19 diagnosis we aimed to include the total number of cases and tests in each country, the number of cases and tests for pediatric ages in each region and the number of pediatric hospitalizations. Table, Supplemental Digital Content 2, http://links.lww.com/INF/E816 summarizes the available data for each site as well as the different sources. Additionally, we retrieved data about SARS-CoV-2 variants, vaccination introduction date and vaccine coverage for adolescents and children from all the participating sites.

Epidemiologic Parameters

The MIS-C incidence is supposed to be primarily affected by the SARS-CoV-2 circulation in a determined region. Therefore, differences in absolute MIS-C trends among countries can vary because of differences in COVID-19 incidences. To avoid such heterogeneity between the countries due to different timeline for the pandemic waves, we assessed the ratio between MIS-C cases and COVID-19 pediatric cases diagnosed 4 weeks earlier (average time for the temporal association observed in this disease) for 5 participating sites [Catalonia (Spain), Chile, Bogotá (Colombia), Costa Rica and The Netherlands]. For 3 other sites where COVID-19 pediatric cases were not available, we assessed the same ratio of MIS-C cases but using the total COVID-19 cases among the general population [Panamá, Ciudad de México and Lazio (Italy)].

As summarized in Table, Supplemental Digital Content 2, http://links.lww.com/INF/E816, not all the countries or areas reported the same data but all of them registered all the MIS-C cases.

Epidemiologic Analysis

First, we plotted the incidence of MIS-C cases per 10^5 inhabitants for children under 18 years for all the regions of study separately and globally and the temporal evolution of monthly MIS-C cases per age-groups (0–2, 3–5, 6–11, 12–17) for each of the participating sites (Supplemental Digital Content 3 and 4, http://links.lww.com/INF/E816).

For the report of the time-series analysis, the ratio between monthly MIS-C cases and monthly COVID-19 cases under 18 years diagnosed in the previous 4 weeks was plotted for the participating sites separately and globally. A probit linear regression model with binomial distribution was performed for each site obtaining the *P* value for the fit to define the statistical significance of the observed trend.

For those sites where pediatric COVID-19 cases were not available, the probit linear regression model was applied to the monthly ratio between MIS-C cases and the total COVID-19 cases reported in the region 4 weeks before [Mexico DF, Panamá and Lazio (Italy)]. The *P* value for the fit was also assessed to define the statistical significance of the observed trend. We finally used the probit linear regression model to predict the MIS-C cases.

The analysis was implemented in MATLAB using the glmfit function for the probit linear regression analysis with binomial distribution for the response variable.[22]

Ethical Issues

This study used aggregated public health data from the health surveillance systems or data from the referral participating hospitals. The study was reviewed and approved by the research ethics committee of the coordinator center with the expedient number PR(AMI)271/2021. All the participating sites obtained their approval by the respective ethics committee for the collection of data related to the MIS-C cases. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. No personal or identifiable data were collected during the conduct of this study.

RESULTS

We collected data of 904 cases of MIS-C, among a reference population of 17,906,432 children aged between 0 and 17 years. The median (interquartile range [IQR]) of the MIS-C cases incidence among the different countries/regions was 0.23 (0.12–0.37) per 100,000 habitants under 18 years old. The number of MIS-C cases per age range per region is shown in Supplemental Digital Content 4, http://links.lww.com/INF/E816. Considering all the sites that provided the age distribution of MIS-C cases, 21.4% [95% confidence interval (CI): 21.2%–21.5%], 20.2% (95% CI: 20.1%–20.4%), 38.3% (95% CI: 38.1%–38.4%) and 20.1% (95% CI: 20.0%–20.3%) correspond to 0–2, 3–5, 6–11 and 12–18 years old, respectively.

Supplemental Digital Content 5, http://links.lww.com/INF/E816, shows the monthly evolution of MIS-C cases for all the

participating sites of this study. It also shows the number of MIS-C cases predicted by the binomial regression from the pediatric (or total) COVID-19 cases in the previous month. The predictions seem to correctly reproduce the global dynamics of MIS-C cases in each site except for some 1-month spikes. This can be related with the time window that is used, that is, a few cases in the beginning or at the end of a month can artificially increase the incidence for that month, while the previous/subsequent one would show an artificial decrease.

Supplemental Digital Content 6, http://links.lww.com/INF/E816, shows the monthly evolution of the ratios between monthly MIS-C cases and the COVID-19 pediatric (or total) cases the month before. Note that the values of the ratios cannot be compared from site to site, since they are affected by the reference region that is chosen for the evaluation of the COVID-19 pediatric (or total) cases. In some sites, MIS-C cases belong to a specific reference hospital, while the region with available epidemiologic data is wider. Moreover, different diagnosis protocols for pediatric COVID-19 cases result in different diagnosis efforts, which make this ratio comparison even more difficult. What we aimed to evaluate is the trend, which is expected to be independent of the region's size and the diagnostic effort, as long as there were not big changes on the diagnostic protocols.

We observed a global significant decreasing trend with the time-series binomial analysis for the ratio between MIS-C cases and COVID-19 diagnosed cases in the previous month ($P < 0.001$). When analyzing each of the participating sites, Chile and The Netherlands kept a significant decrease trend ($P < 0.001$), but this trend was not statistically significant for Catalonia (Spain), Bogotá (Colombia), Costa Rica, Lazio (Italy), Mexico DF or Panamá, although it was observed a not increased trend along the time of the study period (Supplemental Digital Content 6, http://links.lww.com/INF/E816).

To contextualize these results, we included information regarding vaccination start dates and fully vaccination coverage for the age-groups among the participating sites at the end of the study period (Figure, Supplemental Digital Content 7, http://links.lww.com/INF/E816).

Finally, Figure, Supplemental Digital Content 8, http://links.lww.com/INF/E816, shows the SARS-CoV-2 variants predominance per region of study per semester (July 2020–December 2020, January 2021–June 2021 and July 2021–November 2021).

DISCUSSION

In this study, we analyzed the trend of MIS-C diagnoses between July 2020 and November 2021 from an international cohort of children. The data were collected from referral hospitals from 8 different countries or regions, covering an overall reference population of 17,906,432 children aged between 0 and 17 years. Overall, we found that, despite the number and relative contribution of worldwide new pediatric SARS-CoV-2 infections having been progressively increasing during the pandemic, the number of MIS-C cases did not follow a similar pattern, as theoretically expected.

We observed a global significant decrease in trend with the time-series binomial analysis for the ratio between MIS-C cases and pediatric COVID-19 diagnosed cases in the previous month ($P < 0.001$). When analyzing separately each of the participating sites, Chile and the Netherlands maintained a significant decrease in trend ($P < 0.001$), but this ratio was not statistically significant for Catalonia (Spain), Bogotá (Colombia), Costa Rica, Lazio (Italy) or Mexico DF (Supplemental Digital Content 6, http://links.lww.com/INF/E816). Panamá also showed a significant decrease in trend ($P < 0.001$), but this result was for the ratio between MIS-C cases and the COVID-19 cases in the general population (Supplemental Digital Content 6, http://links.lww.com/INF/E816). These different results across the countries or sites could be associated with the sample size, because the higher the number of MIS-C cases are, the better the binomial regression analysis fits with the decreased trend, as shown when we include all the sites at once. Additionally, the decrease through time in the MIS-C to cases ratio in The Netherlands or Catalonia could also be partly due to changing testing strategies during the course of the pandemic, with schoolchildren rarely being tested for SARS-CoV-2 in the beginning and routinely screened bi-weekly in the later months and mainly during the school-periods.[23]

The main finding of the study is particularly relevant if we consider that the majority of countries have introduced mRNA and/or inactivated vaccines against COVID-19 in children 12–17 years of age since mid-2021, suggesting that vaccination could have an impact not only in preventing severe pediatric COVID-19[24] but also MIS-C. Furthermore, different coverage of fully COVID-19 vaccination in adolescents and children in the participating sites could explain the differences of the trend observed between Chile and The Netherlands, with a good coverage at the end of the study period (86% and 62%, respectively),[25,26] and Colombia, with a low fully vaccinated coverage for their adolescents (30%) in November 2021, or Costa Rica, where the vaccination just started on October 25, 2021. These findings are in line with 2 recent studies from France[27] and the United States.[28] In France, no new MIS-C cases were detected in fully vaccinated children 12–17 years of age since September 1, 2021. Similarly, in the United States, 95% of children 12–17 years old with an MIS-C diagnosis since July 1, 2021, were unvaccinated. Considering that France and the United States were not included in our study, our findings could contribute to the current literature that SARS-CoV-2 vaccination might have a significant effect in the prevention of MIS-C. Furthermore, the impact of the vaccines on viral transmission in the community depends on the vaccination coverage, dosage and schedules, as well as type of vaccines administered in the adolescents but also in the adults. The vaccination in the households reduces SARS-CoV-2 transmission in familiar contacts and may also contribute to reducing MIS-C cases.

Although vaccinations seem to play a role in changing epidemiology of MIS-C,[27,28] other hypotheses cannot be excluded, such as the reduction in the number of children who are non-naive to SARS-CoV-2. Interestingly, we found that most centers also reported a reduction in the number of new MIS-C diagnoses in children not yet eligible for vaccination. This observation suggests that other factors, not only vaccination, may contribute to change MIS-C epidemiology. In a recent publication, Professor Brodin hypothesized that a stronger stimulation of immune responses during acute SARS-CoV-2 infection seen with the delta variant may lead to a better viral clearance and, therefore, less persistence in sanctuaries, including the gut.[29] In fact, viral persistence has been documented in the gut months after infection,[30] and Yonker et al demonstrated that in children with MIS-C, a prolonged presence of SARS-CoV-2 in the GI tract led to the release of zonulin, a biomarker of intestinal permeability, with subsequent trafficking of SARS-CoV-2 antigens into the bloodstream, leading to hyperinflammation.[31]

Also, multiple exposure to viable viruses can prime immune responses as happens in rheumatic fever, leading to a postinfectious dysregulated immune response weeks after initial infection.[32] In fact, recent hypothesis states that continuous and prolonged exposure to the viral SARS-CoV-2 superantigen may promote autoimmunity leading to the development of postacute COVID-19 syndromes, including MIS-C and long COVID, as well as the neurologic complications resulting from SARS-CoV-2 infection.[33] A new global scenario characterized by a growing amount of vaccinated people can, in theory, affect the probability of young people

to encounter viable viruses. In fact, recent studies have demonstrated that vaccinated people clear the infection faster from the nasopharynx.[34] This factor can reduce the probability of children to be exposed multiple times to the virus and prime their immune response.

The strengths of the study are the effort in a short time made by an international network of pediatricians sharing data from referral sites and belonging to not only different continents but also different hemispheres, including low-to-middle income countries; and the large sample size of MIS-C cases that led us to demonstrate a significant decrease trend in the time-series analysis for the ratio between MIS-C and COVID-19 cases. In fact, the estimated incidence for MIS-C obtained in the study is very similar to the previously described in United States.[20] To our knowledge, this is the first multinational attempt to describe the trend of the MIS-C incidence during the pandemic.

However, our study has some limitations; first, we were unable to obtain the overall MIS-C cases at the national level for all the countries. Therefore, some cases might have been missed and incidence may be underestimated. However, for other sites, we could collect data for the geographical areas and approximate population covered. Also, hospitals involved were all referral centers for the geographical areas, therefore it is unlikely that MIS-C have been missed or referred to other hospitals. Second, we were unable to detect the monthly number of COVID-19 cases, adult and pediatric vaccinations administered in each country during the pandemic. This limited our possibility to define more strongly the temporal changes of MIS-C diagnoses according to age-specific new SARS-CoV-2 infections and vaccination coverage in adults and children. Third, the observed decreasing trend in the ratio between MIS-C cases and COVID-19 pediatric (or total) cases could be affected by a constant increase in the diagnostic rate of COVID-19; nevertheless, the consistency between different sites, including those that are not considered significant because of the low numbers, suggests that the observed decreasing trend is robust enough. Last, not all centers were able to report the exact percentage of variants circulating each month. Therefore, we could not precisely correlate the temporal variation of MIS-C diagnoses with main local variant circulation. However, considering the current prevalence of omicron variant among the pediatric population, there is a need for further studies to analyze this ratio with this variant of concern.

In conclusion, this study shows a global reduction in the trend of the ratio between MIS-C cases and COVID-19 diagnoses, suggesting that vaccinations may have played a primary role in preventing new MIS-C cases. However, other factors, possibly linked to the virus and/or community transmissions, may be implicated.

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