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ORIGINAL ARTICLE

Pediatric inflammatory multisystemic syndrome in Brazil: sociodemographic characteristics and risk factors to death

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Abstract
Objective: To determine the incidence of MIS-C in Brazil, describe the clinical and sociodemographic characteristics of the pediatric population affected by MIS-C and compare mortality and lethality outcomes with isolated Covid-19 and MIS-C cases.
Methods: Observational and retrospective cohort study of cases of MIS-C associated with Covid-19 in the Brazilian population between 04/01/2020 and 04/17/2021. Data from the Ministry of Health's epidemiological bulletin up to the 15th epidemiological week of 2021, were used. The analyzes were descriptive through absolute and relative frequencies. The significance level is 5% in Stata 16.0 package.
Results: Between 04/01/2020 and 04/07/2021, 903 cases of MIS-C associated with Covid-19 were notified in Brazil, of which, the largest part (55.26%) were male, between 0 and 4 years old (45.29%), from the Southeast region (38.76%). The deaths (61; 6.7%) were higher in the female gender, between 0 and 4 years old (47.54%) and in the Southeast region (34.43%). It was identified that the risk of death by MIS-C related to Covid-19 is 5.29 (CI = 2.83; 9.87 and P-value = <0.001) times higher in adolescents from 15-19 years old than in other age groups when compared to 0-4 years old children. Also, the residency in North region was as risk factor to death (RR = 3.72, IC = 1.29; 10.74 e P-value = 0.008).

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Conclusion: In this study, despite the numbers showing more deaths from zero to 4 years old, the risk for teenagers is notably higher. In addition, Brazil's Northern region is a risk factor that reaffirms social inequality and poor access to health.

Introduction

Since the new coronavirus, SARS-CoV-2, in December 2019 in Wuhan, China, and the COVID-19 pandemic that followed, it was realized that children were proportionally less affected by the disease than adults, presenting, when symptomatic, a usually benign course.[1,2] The situation gained a new perspective when, at the end of April 2020, an alert was issued by the United Kingdom notifying about a new clinical presentation in children and adolescents, possibly associated with COVID-19, Multisystem Inflammatory Syndrome in Children (MIS-C) temporarily associated with COVID-19. After issuing the alert, other countries identified the same syndrome, such as the United States, Spain, and France.[1–3]

MIS-C can occur in healthy children or those with preexisting chronic diseases.[4] The clinic is very similar to Kawasaki Disease (K.D.), a vasculitis of small and medium vessels of unclear etiology and whose most feared complication is the formation of coronary aneurysms.[2] However, significant differences were observed between MIS-C and K.D. Although rare, MIS-C often evolves into a severe form requiring admission to the intensive care unit and may progress to death.[1,2,5] It occurs days to weeks after acute SARS-CoV-2 infection and affects mainly school children and adolescents. It presents more exuberant inflammatory markers and significant elevations of cardiac lesion markers,[3] with a higher frequency of severe myocarditis and/or pericarditis,[1] in addition to abdominal pain and diarrhea proportionally more frequent than in Kawasaki Disease.[1] The first case series published by the United Kingdom showed that all eight patients aged between 4 and 17 years had severe disease, seven progressed to shock and required mechanical ventilation. 75% of the patients were of Afro-Caribbean descent and 62.5% were male; a 14 years old boy, Afro-Caribbean and BMI of 33kg/m^3, with no other comorbidities, was the only one to have a fatal outcome, the cause of death being middle cerebral artery and anterior cerebral artery ischemic infarction.[2,4]

From the perspective of a global panorama, since the end of 2020, there have been increasing reports in Europe, North America, Latin America, and Asia describing the MIS- C associated with COVID-19 in children and adolescents; most of them were restricted to case series.[6] In the U.K., in April 2020, more than 100 children were hospitalized weekly for MIS-C, and it is estimated that one in 5,000 children developed the new syndrome after Covid-19.[7] In the U.S.A., the Center for Disease Control (CDC) partnered with six children- s hospitals to analyze medical data of patients aged < 18 years with COVID-19-related hospitalizations in July and August 2021. Among 915 patients identified, 713 (77.9%) had COVID-19 as the primary cause of hospitalization and 25 (2.7%) had MIS-C. 38.1% of the 713 were aged 12-17 years and 67.5% of the patients had at least one comorbidity, obesity being the most common among 12-17 years old (61,4%). It is also important to say that only one out of 272 vaccine-eligible (aged 12-17 years) patients were fully vaccinated.[8]

In Brazil, since July 2020, notification of the MIS-C temporarily associated with COVID-19 is mandatory, within 48 hours of service, following the standardized form available at the link http://is.gd/simpcovid, under the Technical Note No. 14/2020, published on July 24, 2020, by the Ministry of Health (MS).[9–11] Furthermore, the MIS-C case must also be notified in SIVEP-Gripe.[10] Table 1 shows the Diagnostic Criteria for MIS-C temporally associated with COVID-19.

In Brazil, from April 1, 2020, to March 13, 2021 (Epidemiological Week 10/2021), 813 confirmed cases of MIS-C temporally associated with COVID-19 were reported in children and adolescents aged 0-19 years. There was a predominance in younger children, aged 0 to 4 years (41.9%) and 5 to 9 years (34.3%), and in males (56.7%). Of the cases, 51 progressed to death (6.3%), and 47.1% (n = 24) were children aged 0 to 4 years. There were 26 notifying federated units (U.F.), 17 have death records, and the States with higher confirmed cases notified were São Paulo, Pará, and Bahia.[5]

Of all reported cases, about 29% had some preexisting comorbidity (not specified in the document) and more than 61% of patients required admission to the intensive care unit (ICU).[5] The most commonly reported symptoms were gastrointestinal, present in about 78% of cases. In addition, about 63% of patients had respiratory symptoms, 55% of patients had a skin rash, and evidence of coagulopathy (due to Prothrombin Time, Partial Thromboplastin Time Test, or D-dimer alteration) was present in 53% of cases, 40% had conjunctivitis, 39% developed cardiac dysfunction, 35% had hypotension or shock and 30% of patients had neurological alterations such as headache or mental confusion.[5]

The diagnostic determination of MIS-C has significant clinical relevance since the syndrome imposes an unfavorable outcome on the affected population,[1,2,5] and presents itself as a differential diagnosis of other pathological conditions of interest, such as Kawasaki Syndrome, Incomplete Kawasaki, and Toxic Shock Syndrome.[1] However, at this moment, the research on Sars-Cov-2 infection complications is incipient, with few robust studies on MIS-C, corroborating the need for more studies to determine the incidence of MIS-C, describe the clinical and sociodemographic characteristics of the pediatric population affected it, and compare mortality and lethality outcomes with isolated Covid-19 and MIS-C cases.

Methodology

This research is an observational and retrospective cohort study, based on data from the compulsory notification of

Table 1 Diagnostic Criteria for MIS-C temporally associated with COVID-19.

Diagnostic Criteria for MIS-C temporally associated with COVID-19
Cases hospitalized with the presence of fever (>38 °C) and persistent (≥ 3 days) feverin children and adolescents (up to 19 years old) AND at least 2 of the following signs and/or symptoms;
•Non-purulent conjunctivitis or bilateral skin lesion or signs of mucocutaneous inflammation (oral, hands or feet);
•Hypotension or shock;
•Manifestations of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities [including echocardiogram findings or Troponin elevation, or N- terminal B-type natriuretic peptide (NT-proBNP)];
•Evidence of coagulopathy (by high PT, PTTa or D-dimer);
•Acute gastrointestinal manifestations (diarrhea, vomiting or abdominal pain).
AND
•Elevated inflammation markers (ESR, CRP or procalcitonin...).
AND
•Ruled out any other causes of infectious and inflammatory origin, including bacterial sepsis and staphylococcal or streptococcal shock syndromes
AND
•Evidence of COVID-19 (molecular biology, positive antigenic or serological test) or a history of contact with a case of COVID-19.
Additional comments
•Children and adolescents who meet partial or full criteria for Kawasaki syndrome or toxic shock syndrome may also be included.
•The possibility of MIS-C should be considered in any characteristic pediatric death with evidence of SARS-CoV-2 infection

Brasil. Ministério da Saúde. 2020.

cases of a pediatric multisystem inflammatory syndrome (MIS-C), temporally associated with Covid-19.

The data on MIS-C cases among boys and girls from 0 to 19 years old, living in all the Federated Unities (FU) of Brazil, was extracted from the epidemiological bulletins of the Ministry of Health weekly updated with cases by FU, age groups and sex, grouped and tabulated. Also, the notification on COVID-19 databases of each Federated Unities was downloaded and filtered by the same population characteristics with only confirmed cases or cases with laboratory evidence of the disease used for the statistical analysis. The general population from 0-19 years old data was from the Brazilian Institute of Geography and Statistics (IBGE) projection of population by sex and age group between 2000-2030.

The indicators were calculated as follows:

$$Incidence = \frac{Cases\ of\ the\ disease}{Population\ at\ risk\ of\ the\ disease} \times 100\,000$$

$$Mortality = \frac{Deaths\ by\ the\ disease}{Population\ at\ risk\ of\ diyng\ of\ the\ disease} \times 100\,000$$

$$Lethality = \frac{Deaths\ by\ disease}{Population\ with\ the\ disease\ in\ the\ period} \times 100$$

To calculate the COVID-19 indicators, the general population was considered, and for the MIS-C analysis, the population considered was COVID-19 cases.

There was no need for submission to a research Ethics Committee because it was a study with secondary data that did not identify the participants as per National Health Council (CNS) Resolution No. 466, dated December 12th 2012, and CNS Resolution No. 510, dated April 7th 2016.

Data was tabulated in Excel and the analysis was performed at Stata 16.0 (StataCorp LLC).

Results

Between April 1, 2020 and April 17, 2021 (the 15th epidemiological week of 2021), 903 cases associated with Covid-19 were reported in Brazil, indicating an incidence of 70.21 cases per 100,000 cases of Covid-19. Table 2 shows the demographic characteristics of MIS-C cases and deaths. It is observed that most cases (55.26%) occurred in males, aged between 0 and 4 years of age (45.29%), in the Southeast region (38.76%). Deaths were more frequent in females (54.11%), between 0 and 4 years of age (45.29%), and in the Southeast region (34.43%). It was identified that the risk of death from MIS-C related to Covid-19 is 5.29 (CI = 2.83; 9.87 and p-value $\leq$ 0.001) times higher in adolescents aged 15-19 years when compared to children from 0-4 years. In addition to age group, residence in the North region was a risk factor for death (RR = 3.72, CI = 1.29; 10.74 and p-value = 0.008). The incidence was higher in males (71.62 cases of MIS-CP/100 thousand cases of Covid-19), varying in age groups between 4.32 (15-19 years) and 174.64 (0-4 years) cases/100,000 children and adolescents with Covid-19. It is also worth noting that the lowest and highest incidences occurred in the South and Southeast (31.27 and 103.13 cases/100,000 children and adolescents with Covid-19, respectively).

Table 3 shows Mortality (per 100,000 Covid cases) and Lethality (percentage of Covid cases) data for MIS-C and Covid without SIMP. It is observed that in the MIS-C

Table 2 Demographic characteristics of cases and deaths, incidence and Relative Risk for death of Multisystem Inflammatory Syndrome in Children (MIS-C) associated with Covid- 19 in Brazil.

	Cases	Total cases Covid-19	Incidence[a]	Deaths	RR (IC)	p-value
Sex	N (%)			N (%)		
Female	404 (44.74)	589,450	68.54	33 (54.11)	1	
Male	499 (55.26)	696,717	71.62	28 (45.90)	0.69 (0.42; 1.12)	0.128
Age Group						
0-4	409 (45.29)	234,190	174.64	29 (47.54)	1	
5-9	288 (31.89)	214,945	133.99	13 (21.31)	0.64 (0.34; 1.20)	0.159
10-14	182 (20.16)	278,346	65.39	10 (16.39)	0.77 (0.38; 1.56)	0.470
15-19	24 (2.66)	555,686	4.32	9 (14.75)	**5.29 (2.83; 9.87)**	**<0.001**
Region						
Midwest	94 (10.41)	111,455	84.34	4 (6.56)	1	
North East	240 (26.58)	302,631	79.3	14 (22.95)	1.37 (0.46; 4.06)	0.566
North	101 (11.18)	155,310	65.03	16 (26.23)	**3.72 (1.29; 10.74)**	**0.008**
Southeast	350 (38.76)	339,375	103.13	21 (34.43)	1.41 (0.50; 4.01)	0.515
South	118 (13.07)	377,396	31.27	6 (9.84)	1.19 (0.35; 4.11)	0.777
Total	903 (100.00)	1286167	70.21	61 (100.00)		

Table 3 Mortality and Lethality Coefficients of SIM-P associated with Covid-19 and Covid- 19 in Brazil, by sex, age group and region of residence, Relative Risk and P-value.

	MIS-C	Covid-19	Relative Risk (IC)	p-value
		MORTALITY[a]		
Sex				
Female	5.6	1.07	**5.23 (3.54; 7.50)**	**< 0.001**
Male	4.02	1.19	**3.39 (2.22; 4.98)**	**< 0.001**
Age Group				
0-4	12.38	2.28	**5.43 (3.58; 7.95)**	**< 0.001**
5-9	6.05	0.38	**16.07 (8.05; 29.79)**	**< 0.001**
10-14	3.59	0.56	**6.39 (2.96; 12.31)**	**< 0.001**
15-19	1.62	1.37	1.18 (0.53; 2.29)	0.298
Region				
Midwest	3.59	0.64	**5.60 (1.46; 15.40)**	**0.004**
North East	4.63	1.5	**3.09 (1.67; 5.27)**	**< 0.001**
North	10.3	0.71	**14.47 (8.08; 24.21)**	**< 0.001**
Southeast	6.19	1.75	**3.53 (2.12; 5.61)**	**< 0.001**
South	1.59	1.38	1.15 (0.41; 2.64)	0.353
Total	4.74	1.13	**4.20 (3.18; 5.46)**	**< 0.001**
		LETHALITY		
Sex				
Female	8.17	0.05	**151.31 (107.17; 213.63)**	**< 0.001**
Male	5.61	0.05	**106.16 (69.57; 156.01)**	**< 0.001**
Age Group				
0-4	7.09	0.13	**52.79 (34.78; 77.33)**	**< 0.001**
5-9	4.51	0.03	**176.17 (88.29; 326.63)**	**< 0.001**
10-14	5.49	0.03	**173.68 (80.49; 334.72)**	**< 0.001**
15-19	37.5	0.04	**909.93 (410.82; 1757.90)**	**< 0.001**
Region				
Midwest	4.26	0.04	**110.20 (28.73; 303.23)**	**< 0.001**
North East	5.83	0.09		**< 0.001**
North	15.84	0.11	**149.92 (83.72; 250.86)**	**< 0.001**
Southeast	6	0.04	**148.48 (89.05; 263.08)**	**< 0.001**
South	5.08	0.02	**290.66 (102.96; 667.01)**	**< 0.001**
Total	6.76	0.05	**126.56 (95.76; 164.61)**	**< 0.001**

CI, confidence interval.
[a] Per 100,000 cases of Covid-19 (SIM-P) and 100,000 children and adolescents (Covid-19).

associated with Covid-19, the mortality coefficient was more expressive in females (5.6 deaths/100,000 cases of Covid-19 in children and adolescents), as well as in the age group between 0 -4 years (12.38 deaths/100,000 cases of Covid-19 in children and adolescents) and in the North region (10.3 deaths/100,000 cases of Covid-19 in children and adolescents). Among the Covid-19 cases, removing the MIS-C cases, the mortality was 1.19 deaths/100,000 children and adolescents, with 2.28 deaths between 0 and 4 years, for every 100,000 children and teenagers. Finally, the region with the highest mortality was the Southeast (1.75 cases/100,000 children and adolescents).

MIS-C was associated with higher mortality, when compared to Covid, in all categories (except for the 15-19 years age group and the South region, where they were similar), with females at higher risk (RR = 5.23 and CI = 3.54; 7.50), the age group between 5-9 years (RR = 16.07 and CI = 8.05; 29.79) and residence in the North region (RR = 14.47 and CI = 8.08; 24.21). Regarding lethality, in MIS-C associated with Covid-19, the coefficient was higher in females (8.17%), as well as in the age group between 15-19 years (37.5%) and the North region (15.84%). Among the Covid-19 cases, removing MIS-C cases, lethality was 0.05% in both sexes, with a higher proportion between 0-4 years (0.13%). The region with the highest lethality was the North (0.11%). MIS-C was associated with higher lethality, when compared to Covid-19, in all categories, with a higher risk in females (RR = 51.31 ad CI = 107.17; 213.63), in the age group between 15-19 years (RR = 909.93 and IC = 410.82; 1757.90) and the South region (RR = 290.66 and IC = 102.96; 667.01)

Discussion

In April 2020, the Brazilian Ministry of Health implemented national monitoring of MIS- C, through notification.[10] Up to the 15th Epidemiological Week (S.E.) of 2021, 903 cases of MIS-C were reported in children and adolescents, with a record of 61 deaths, determining a significant lethality of 6.76%.

The analysis of the demographic characteristics described in Table 1, showed that males were more affected, but females had higher lethality. The numerical analysis showed no statistical difference between the groups, which may have occurred due to the small number of cases under analysis since the literature shows the female gender as a risk factor for the outcome mentioned above.[12,13] However, in all variables compared, such as gender, age, or region, lethality was significantly higher than that of COVID-19, establishing the independence of variables to predict the worst outcome of the first compared to the second condition.

Concerning age group, the incidence coefficient was inversely proportional to age, so that the 0-4 years group had 174.64 cases of MIS-C for every 100,000 cases of COVID-19 (with 29 registered deaths), and the group aged 15-19 years presented 4.3 cases of MIS-C for every 100,000 cases of COVID-19 (with 9 registered deaths).

On the other hand, the lethality analysis taking the 0-4 years group as a reference showed the 15-19 years group as a risk factor for death by MIS-C, with a clear statistical difference and a 5.29-fold higher risk. These results corroborate international data and show that adolescents, when affected by MIS-C, have a higher risk of evolving to death.[12,13]

When comparing mortality rates due to MIS-C and COVID-19 in the population aged 0-19 years, the authors observed that MIS-C mortality is significantly higher than that of COVID-19 in the population aged 0-14 years. The group from 5-9 years has the highest RR in this context, although the one with the highest incidence for MIS-C is from 0-4 years. The greater severity of MIS-C in older age groups could be associated with the difference in clinical manifestations according to the age group; in New York, it was shown that children between 0-5 years of age were more affected by dermatological symptoms, while the prevalence of myocarditis was higher in adolescents.[12] Another study, also from the USA, postulates that potential differences between age groups may be due to differences in basal expression of Angiotensin- 2 converting enzyme, receptor used for cell entry by SARS-CoV-2.[14] A cohort of 305 patients, aged 4 to 60 years, older children (10-17 years), young adults (18-24 years), and adults ($\geq$ 25 years) all had higher ACE2 expression in the nasal epithelium than children from 4 to 9 years old.[15]

Compared to other studies, MIS-C mortality rates in Brazil were higher than previous international findings that demonstrated a better long-term prognosis.[16—18] Care must be taken when interpreting these data since most studies described counted with a much smaller population sample. In addition, differences in the pattern of previous comorbidities of patients, the possible differences in the speed of diagnosis, and the quality of management of the syndrome in different locations could contribute to higher rates of unfavorable outcomes.[19]

Knowing that the adolescent age group is a risk factor for tragic outcomes due to MIS- C, it is necessary to understand the disease process of young people and the reasons for their non-adherence to preventive measures for contamination. Adolescence is marked by neurobiological changes in which there is an increase in the importance of relationships with peers and a greater need for social support, which is a factor that hinders adherence to social isolation due to the intense psychological impact. Furthermore, studies show habits that facilitate the transmission of Covid-19 in this age group, such as storing masks in inappropriate places and their repetitive use.[20]

A study carried out with adolescents in Oslo shows that non-adherence to the recommendations to mitigate the pandemic is related to structural factors, such as residential overcrowding and job exposure to the infection. In addition, it was noticed that young people were less careful when the infection was less prevalent in the region but changed their behavior when the spread intensified.[21] Understanding this process is essential for developing potential ways in public health to mitigate this Brazilian health problem.

The present data indicates that living in Brazil's North region is a risk factor for higher Mortality by MIS-C. Taking Midwest Region as a reference, all other regions presented a lethality coefficient without statistical differences, except for the North (OR 3.72). This is an expected result that agrees with what is found in the literature.[22] Such disproportion shows the inequality of access to the health system so that the North region still lacks a universal and

comprehensive care system. North Region's higher Mortality could also be explained by the higher incidence of cases in this location, a finding consistent with international studies, where the regions with the highest Mortality and those with the highest incidence of cases were the same.[20] Extrapolating this data, the North and Northeast regions have the lowest number of hospital beds per inhabitant in Brazil. At the pandemic's beginning, the number of ICU beds per inhabitant in the North region was approximately half of those available in the South region.[23] The precarious installation of the health system in the region would determine care, diagnosis, and treatment measures in a late period, in which the disease would impute more significant morbidity and Mortality, corroborating current evidence.[19]

Limited scientific knowledge, the high speed of virus dissemination, and the potential to cause death in the population raised doubts about the best strategy for coping with the health crisis of Covid-19. Brazil's challenges are even higher due to social inequalities, precarious living, sanitary conditions, and agglomeration. Therefore, knowing the political and social context of the country is of paramount importance to understanding the panorama of the pandemic and the disastrous proportions that MIS-C can reach. Unfortunately, there has been a denial policy, with unscientific measures adopted during the Covid crisis, which led the country to many infected people and deaths compared to other nations.[24]

World data with lethality of 1.5% are very discrepant compared to Brazil data, showing the long road ahead for the country to face the pandemic.[25] It is noticeable that there are still many variables to be studied about the involvement of children and adolescents with MIS-C. In addition to gaps in the pathophysiology of the disease in this age group, it is necessary to consider the substantially new scenario in which the authors are inserted.[26]

This study has limitations, including using secondary data, subject to possible biases related to data collection and measurement, possibly making them of lower quality. In addition, notification bias was crucial in the case of MIS-C, despite the implementation of national monitoring as of 07/24/2020 and the recommendation of notification of cases, including retroactive ones. Furthermore, there can still be substantial underreporting of cases due to the widespread lack of knowledge of the syndrome by health professionals and its temporality since it can occur days to weeks after the acute flu syndrome by COVID-19 most of these children do not maintain post-disease follow-up.[10]

Another limitation was concerning the study design, and as it is a retrospective observational Cohort, it was not possible to remove all possible confounding factors. Finally, the inconvenience regarding the possible overestimation of the relative risk of death from MIS-C was identified, given the critical underreporting of cases of death from COVID -19 in the country, mainly in poorer regions, and better monitoring of MIS-C cases in Brazil (due to the lower incidence and more marked manifestations), making the lethality rate from this syndrome more reliable.[27]

This study shows that Mortality and lethality due to MIS-C are higher in Brazil than those found in other countries, with even worse outcomes in adolescents and residents of the North region. These data point to the urgent need for treatment protocols for this syndrome for better management and outcomes. In order to avoid the worsening of this scenario in the country, it is up to health authorities to develop public policies aimed at reducing the spread of the virus in these age groups, alerting society, disseminating quality scientific information for health professionals, as well as more studies on MIS-C and the availability of resources for its treatment, so that we do not lose more lives to this sad situation.

Conflicts of interest

The authors declare no conflicts of interest.

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