Síndrome multissistência inflamatória em crianças (MIS-C) associada à infecção pelo novo vírus SARS-COV-2 relato de casos de um hospital pediátrico no sul do Brasil

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RESUMO
Objetivo: Descrever as características clínicas, epidemiológicas e a evolução de pacientes pediátricos com diagnóstioco de Síndrome multissistêmica inflamatória em crianças (MIS-C) associada ao novo coronavirus, SARS-CoV-2, em um hospital terciário do sul do Brasil. Métodos: Relatamos uma série de casos retrospectivos de pacientes com menos de 14 anos de idade admitidos em nosso hospital no periodo de 10 de março a 31 de dezembro de 2020. O diagnostic foi realizado de acordo com os critérios do Centro para Controle e Prevenção de Doenças dos Estados Unidos (CDC) e da Organização Mundial da Saúde (OMS). Os dados foram coletados de prontuário médico eletrônico. Resultados: Durante o período do estudo, 9 pacientes pediátricos foram incluídos. A mediana de idade foi de 9 anos (6-11), 78% eram do sexo masculino, 55% tinham comorbidades (3 eram obesos e 2 tinham história de asma leve). Todos os pacientes tinham febre, 89% tinham sintomas gastrointestinais, 67% tinham envolvimento mucocutâneo, 44% tinham alterações cardiovasculares e 33% tinham sintomas respiratórios leves. Seis (67%) foram internados na UTIP. Nenhum paciente necessitou de ventilação mecânica e não houve óbitos. Conclusões: MIS-C é uma nova síndrome descrita em crianças e jovens associada a COVID-19 que deve ser lembrada como hipótese diagnóstica em qualquer paciente com febre persistente e sintomas multissistêmicos. Apesar da gravidade, a resposta à terapia parece ser boa, com baixa mortalidade.
Palavras-chave: infecções por coronavírus; COVID-19; crianças; cuidados intensivos pediátricos.

Multisystem inflammatory syndrome in children (MIS-C) associated with infection by the new SARS-COV-2 virus: a report of cases in a pediatric hospital in southern Brazil

ABSTRACT
Objective: To describe the clinical and epidemiological characteristics and the evolution of pediatric patients with diagnoses of the multisystem inflammatory syndrome in children (MIS-C) associated with the new coronavirus, SARS-CoV-2, in a tertiary hospital in southern Brazil. Methods: We report a series of retrospective cases of patients younger than 14 years old admitted to our hospital from March 10 to December 31, 2020. The diagnosis was carried out according to the criteria of the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). The data were collected from electronic medical records. Results: During the study period, nine pediatric patients were included. The age median was 9 years (6 to 11), with 78% male and 55% having comorbidities (three were obese, and two had a history of mild asthma). All patients had fevers, 89% had gastrointestinal symptoms, 67% had mucocutaneous involvement, 44% had cardiovascular alterations, and 33% had mild respiratory symptoms. Six (67%) were admitted to the PICU. None of the patients needed mechanical ventilation, and there were no deaths. Conclusions: The MIS-C is a new syndrome described in children and youths associated with COVID-19 that must be considered a diagnostic hypothesis for any patient with persistent fever and multisystem symptoms. Despite the severity, the response to therapy seems to be good, with low mortality.
Keywords: coronavirus infections; COVID-19; children; pediatric intensive care.

1. INTRODUCTION

In April 2020, initially in Europe, there was an increase in the description of cases of children with multisystem involvement severe illness, apparently associated to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (VERDONI *et al.*, 2020; RIPHAGENS *et al.*, 2020; GRIMAUD *et al.*, 2020). The Royal College of Paediatrics and Child Health, (2020) in the UK published a definition of the so-called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in May 2020. On May 14, the U.S. Centers for Disease Control and Prevention (CDC), (2020) described the new illness and named it multisystem inflammatory syndrome in children (MIS-C), and on May 15, 2020, the World Health Organization (WHO) (2020), issued an alert for the new syndrome requesting international collaboration for case reporting.

Although there are differences in definitions, the so-called MIS-C is characterized by fever, elevated inflammatory markers and multisystem organ involvement, associated with the evidence of exposure to or infection with the SARS-CoV-2 virus (FELDSTEIN *et al.*, 2020; GOLDFRED-CATO *et al.*, 2020; KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021; KABEERDOSS *et al.*, 2021). More than 1000 cases have been reported in several countries around the world with different phenotypes (KABEERDOSS *et al.*, 2021; ESPOSITO; PRINCIPI, 2021; DAVIES *et al.*, 2020; NAKRA *et al.*, *2020;* TULIE *et al.,* 2020; WEBB *et al.*, 2020; WHITE *et al.*, 2020; TORRES *et al.*, 2020; MAHMOUD *et al.*, 2021). Although the first cases described severely compromised children, based on the diagnostic criteria, the syndrome may include children with milder conditions, such as a febrile inflammatory state. The clinical manifestations described are variable, ranging from Kawasaki-like disease or a severe form of MIS-C associated with cardiac involvement and shock. Cases have also been described where the manifestations of severe COVID and MIS-C overlap (FELDSTEIN *et al.*, 2020; GOLDFRED-CATO *et al.*, 2020; KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021). In most cases, MIS-C appears to be a post-infectious complication, but in some patients the symptoms

described in MIS-C seem to occur during the SARS-CoV-2 infection acute phase (GOLDFRED-CATO *et al.*, 2020; ESPOSITO; PRINCIPI, 2021).

Brazil is one of the countries more affected by the pandemic in the world and we believe that the description of our patients can contribute to the construction of knowledge about this new disease. This retrospective case series describes the clinical and epidemiological characteristics and evolution of pediatric patients under 14 years old in a tertiary care hospital in southern Brazil.

2. METHOD

We reported a retrospective descriptive observational study (case series) of pediatric patients diagnosed with MIS-C on admission or during hospitalization at Hospital Criança Conceição, from March 10, 2020 to December 31, 2020. Cases were located through search in diagnostic database. After selection, the electronic medical records were reviewed in detail, the necessary data collected and the standardized protocol completed. Data collection was performed by two physicians who had been previously trained by the main researcher to complete the study protocol. All patients had their records evaluated until hospital discharge.

The included patients ranged in age from 1 month to 14 years and met the definition criteria for MIS-C according to the World Health Organization, (2020) and the Centers for Disease Control and Prevention Alert Network, (2020). The diagnosis of SARS-CoV-2 infection was made by positive SARS-CoV-2 serology (IgG or IgM) or positive real time reverse transcriptase polymerase chain reaction (RT-PCR) result for SARS-CoV-2 on a nasopharyngeal swab. We collected data regarding epidemiological characteristics, clinical presentation, laboratory and imaging tests, treatment, evolution, and outcome.

Hospital Criança Conceição is a training center for doctors, being a reference hospital for the care of highly complex patients. Our hospital is a regional reference in the care of children diagnosed with COVID-19.

The data from electronic medical where recorded them in a Microsoft office Excel 2010 spreadsheet. We presented categorical variables as proportion (%) and

expressed continuous data as median and interquartile range (IQR). This study was approved by the Research Ethics Committee of Hospital Group Conceição, evaluation number 4.421.334.

3. RESULTS

During the study period, nine children were hospitalized with MIS-C criteria. Six patients were diagnosed with SARS-CoV-2 infection by serology and one by RT-PCR and serology. We included in the study a 12-year-old girl, who developed an incomplete Kawasaki disease and reported contact with her grandfather (hospitalized in the ICU for COVID-19) 60 days prior to the clinical presentation onset and had negative RT-PCR and serologies. We also included in the analysis an 11-year-old boy, who was admitted with appendicitis suspect and evolved with MIS-C criteria overlapped on Kawasaki disease, with negative RT-PCR and serology and no history of contact with infected patient. Table 1 describes the patients clinical and epidemiological characteristics.

Table 1- Clinical and epidemiological characteristics

Age, years median (IQR)	9 (6-11)
Age, n (%) 3 - 5 years 6 - 10 years 11 – 14 years	 2 (22%) 4 (44%) 3 (33%)
Sex, male n (%)	7 (78%)
Ethnicity white n (%)	9 (100%)
Comorbidities, yes n (%)	5 (55%)
Specific comorbidity n (%) obesity mild asthma	 3 (33%) 2 (22%)
Known contact with a COVID-19 case yes n (%)	5 (55%)
Duration of symptoms before hospitalization, days median (IQR)	6 (3-6.5)
Symptoms on admission n (%) fever vomiting abdominal pain prostration conjunctivitis loss of appetite	 9 (100%) 8 (89%) 7 (78%) 6 (67%) 6 (67%) 5 (55%)

headache	4 (44%)
skin rash	4 (44%)
diarrhea	3 (33%)
cough	3 (33%)
cutaneous sings inflammation (hands and feet)	3 (33%)
mucous oral changes	
myalgia	2 (22%)
odynophagia	1 (11%)
arthralgia	1 (11%)
poor perfusion	1 (11%)
	1 (11%)

IQR=Interquartile range, n=number of patients
Data source: Produced by the authors.

Five patients (55%) reported previous contact with an individual with confirmed COVID-19. In four cases the contact was with a family member at home. Only one patient had a history of a viral presentation compatible with SARS-CoV-2 infection two months before the current diagnosis. Although 5 (55%) of the patients had comorbidities (three children were obese and two children had a history of mild asthma), the patients reported no previous hospitalizations and none of them chronically used medications.

Six (67%) of the patients had MIS-C criteria on admission. Another three children had persistent fever and developed new symptoms during hospitalization, presenting MIS-C criteria from the second to the third day of hospitalization (two children developed cutaneous rash and mucocutaneous changes and one presented shock). Of the nine patients included in the study, one child had MIS-C criteria overlapping with Kawasaki disease, three had MIS-C criteria, and five patients had criteria compatible with incomplete Kawasaki, with two patients having a Kobayashi score > or equal to 5 (KOBAYASHI *et al.*, 2006).

Table 2 describes the laboratory findings on admission and the treatment performed. The total leukocytes number was normal in eight (89%) of the patients and only one had leukocytosis.

Table 2- Laboratory findings and treatment

	Reference ranges	Median (IQR)	Patient 1	Patient 2	Patient 3	Patient 4	Patient5	Patient 6	Patient 7	Patient 8	Patient 9
neutrophil /uL	2000-8000	5000 (4100-8185)	12500	4000	8370	4200	4000	8000	4500	5000	5800
lymphocytes /uL	1500-4000	1450 (910-1850)	1630	1900	1450	2100	970	1800	1400	250	850
hemoglobin g/dl	13-15	10 (9.8-10.9)	9.3	9.8	10	9.9	10.9	11	10.9	10.1	10
platelets /uL	150,000-400,000	175000 (95500-230000)	118000	175000	200000	45000	73000	260000	179000	163000	310000
CRP mg/L*	<5	140 (107-173)	175	96	173	160	174	119	29	130	140
D-Dimer ng/mL*	<500	2280 (1880-4792)	1850	2230	2000	4650	4840	2330	16700	1200	5560
ferritin ng/ml*	>500	461 (330-1370)	1370	330	660	460	1970	450	181		714
LDH U/l*	240-480	532 (485-733)	742	544	706	520	488	440	960	484	423
troponin T ng/L*	<14	17 (9.6-46)	46	15	18		17	95	5.2	9.6	
sodium mEq/L	135-145	135 (129-136)	129	137	139	130	131	135	136	136	129
triglycerides mg/dl*	<150	210 (157-434)		210	164		588	280	150		
fibrinogen mg/dl*	200-393	378 (336-487)	334	360	598	396	500	284	344	450	691
albumin g/dl*	3.5-5	2.9 (2.6-3.2)	2.5	3.2	3.1	2.7	2.8	2.6	3.6	3.1	
AST U/L*	<37	59 (29-107)	68	33	27	186	58	60	120	28	59
creatinine mg/dL*	0.4-1.1	0.54 (0.35-0.6)	0.58	0.37	0.34	0.3	0.97	0.5	0.6		0.6
INR*	0.9-1.1	1.2 (1.2-1.3)	1.2		1.2	1.2	1.1	1.2	1.2	1.6	1.4
SARS-Cov-2 infection			IgG positive PCR	IgG and IgM	IgG positive PCR	IgG and IgM positive	IgG and IgM	IgG and IgM positive	PCR and serology	PCR and IgG	PCR and serology

diagnosis			negative	positive PCR negative	negative	PCR negative	positive PCR negative	PCR negative	negative (COVID-19 exposure)	and IgM positive	negative
antibiotics			oxacillin cefepime	ceftriax	ceftriax	ceftriax oxacillin	ceftriax clindamycin	-	ceftriax	vanco cefepime	ceftriax
volume expansion	yes									yes	yes
vasopressor support										yes	
IVIG			yes			yes	yes	yes	yes	yes	yes
corticosteroidis				yes	yes pulse	yes	yes pulse	yes	yes	yes pulse	yes pulse
aspirin			yes			yes	yes	yes	yes	yes	yes
anticoagulation			yes				yes	yes	yes	yes	

IQR= interquartile range, CRP=C-reactive protein, AST=aspartate aminotransferase, LDH=lactate dehydrogenase, INR international normalized ratio, IgG =immunoglobulin G, IgM= immunoglobulin M, PCR= polymerase chain reaction, IVIG=human intravenous immunoglobulin, vanco= vancomycin, ceftriax=ceftriaxone, * tests required on admission or at the time of MIS-C suspected diagnosis
Data source: Produced by the authors.

Regarding coinfection, 88% of the patients had blood cultures collected and only one child had a positive blood culture for an unidentified gram positive sporulated bacillus. Four patients had urine cultures taken, all with negative results, and two patients had cerebrospinal fluid cultures also negative. Four patients presented respiratory symptoms, and research for respiratory viruses (adenovirus, respiratory syncytial virus, influenza A and B, parainfluenza I, II, and III) were collected by direct immunofluorescence and RT-PCR for influenza, all tests were negative.

Table 3 shows data regarding imaging exams and patients evolution. Six patients (67%) were admitted to the PICU, four for monitoring and two for shock. Four patients (44%) received oxygen therapy. In our case series no patient required mechanical ventilation. Three patients received fluid resuscitation with crystalloids bolus during hospitalization for altered perfusion or hypotension, but only one child required vasoactive drugs (adrenaline). Although four patients (44%) had impaired kidney

function on admission, none required renal replacement therapy. Eight children (89%) received empirical antibiotic therapy. Seven patients (78%) used immunoglobulin, and in 6 cases, corticosteroids were also prescribed.

Table 3 – Findings imaging, treatment, and outcome

chest x-ray/chest computed tomography n (%)	
normal	3 (33%)
bilateral infiltrate	1 (11%)
focal consolidation and pleural effusion	1 (11%)
bilateral infiltrate and pleural effusion	2 (22%)
electrocardiogram n (%)	
normal	8 (88%)
echocardiography n (%)	
normal	6 (67%)
pericardial effusion	1 (11%)
coronary dilatation, mitral regurgitation, and pericardial effusion	1 (11%)
abdominal ultrasound n (%)	
adenopathy mesenteric and free fluid	3 (33%)
hepatosplenomegaly	1 (11%)
mesenteric adenitis	1 (11%)
ileitis and free fluid	2 (22%)
organ-system involvement n (%)	
two systems	3 (33%)
three systems	3 (33%)
four or more systems	3 (33%)
PICU admission n (%)	6 (67%)
PICU length of stay, days median (IQR)	3.5 (2-8)
length of stay, days median (IQR)	10 (5.5-15)
mortality	0

n = number of patients, PICU= Pediatric Intensive Care Unit, IQR=Interquartile range
Data source: Produced by the authors.

No patients received antiviral therapy or biologic agents. Five children (55%) received enoxaparin, four in prophylactic dose and one in treatment dose. No hemorrhagic events have been reported. One child, without comorbidity, presented cephalic vein thrombosis in the proximal third of the forearm and in the distal third of the right arm during hospitalization. All children progressed well, with a median hospital stay of 10 days. No deaths have been reported.

4. DISCUSSION

In our case series, almost 80% of the patients were male. Most studies describe a slight predominance of boys affected by the disease (FELDSTEIN *et al.*, 2020; KAUSHIK *et al.*, 2020; FERNANDEZ-SARMENTO *et al.*, 2021; DAVIES *et al.*,

2020). Our median age was 9 years, the median age described in the literature ranges from 8 to 11 years, but there are cases described in infants and in adults (FELDSTEIN *et al.*, 2020; GOLDFRED-CATOS *et al.*, 2020; KAUSHIK *et al.*, 2020; KABEERDOSS *et al.*, 2021; DAVIES *et al.*, 2020). It is thought that this new disease spectrum may affect any age group. Studies describe an apparent predominance of the syndrome in black and hispanic children (FELDSTEIN *et al.*, 2020; GOLDFRED-CATOS *et al.*, 2020; KAUSHIK *et al.*, 2020). However, in our small sample all patients were white. Southern Brazil had strong european colonization, with a more than 80% white population. The extent to which this difference reflects genetic predisposition or socioeconomic issues still needs further investigation (GOLDFRED-CATOS *et al.*, 2020; ESPOSITO; PRINICPI, 2021; DAVIES *et al.*, 2020). Although in our sample 55% of the children had comorbidities, we observed only obesity and mild asthma, and no patients had a history of prior hospitalization. MIS-C seems to affect more previously healthy patients (KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021, DAVIES *et al.*, 2020; NAKRA *et al.*, 2020). Several studies have described obesity as the main comorbidity associated with MIS-C, followed by respiratory diseases such as asthma (GOLDFRED-CATOS *et al.*, 2020; KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021). Interestingly, in our sample, no patients had a history of chronic medication use.

Most children had 6 days (median) of symptoms before hospitalization. Studies have noted 4 to 5 days of symptoms before hospital admission (KAUSHIK *et al.*, 2020; KABEERDOSS *et al.*, 2021). All of our patients had persistent fever, other common symptoms were abdominal pain and vomiting, followed by mucocutaneous symptoms (conjunctivitis and rash). In five patients the abdominal condition was the reason for hospitalization, three of these had suspected appendicitis. There are case series of children with MIS-C unnecessarily submitted to exploratory laparotomy (KABEERDOSS *et al.*, 2021; ESPOSITO; PRINICPI, 2021; WEBB *et al.*, 2020). In our study 4 (44%) of the patients that had cardiovascular changes, two patients had significant troponin increase, with no changes in the echocardiogram, and another two had abnormal echocardiogram (one with pericardial effusion and the other with

coronary dilatation, pericardial effusion, and mitral regurgitation) both with borderline troponin. Only one of these patients required vasoactive drugs due to a shock. Studies have described fever, gastrointestinal, mucocutaneous and cardiovascular symptoms as the most common symptoms (GOLDFRED-CATOS *et al.*, 2020; KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021; ESPOSITO; PRINICPI, 2021). In a meta-analysis (KAUSHIK *et al.*, 2020), (655 patients), 70% of patients had gastrointestinal symptoms, 51% had cardiovascular symptoms, 36% had symptoms described in Kawasaki disease, and most commonly (82.5%) symptoms were compatible with incomplete Kawasaki disease. Although respiratory symptoms are common, the percentage of patients with severe respiratory impairment requiring mechanical ventilation is low (FELDSTEIN *et al.*, 2020; GOLDFRED-CATOS *et al.*, 2020; KAUSHIK *et al.*, 2020). Most intubated children present shock as the cause of intubation (FERNANDEZ-SARMIENTO *et al.*, 2021; DAVIES *et al.*, 2020). Studies have observed that, even in patients without characteristics compatible with Kawasaki disease, there is an increased risk of cardiac disease, both at hospital admission and during hospitalization, and cardiac follow up is recommended in all patients diagnosed with MIS-C (FELDSTEIN *et al.*, 2020; GOLDFRED-CATOS *et al.*, 2020; KABEERDOSS *et al.*, 2021) Between 6 and 24% of patients with MIS-C have developed coronary artery disease, which can occur after the resolution of the syndrome's symptoms (FERNANDEZ-SARMIENTO *et al.*, 2021; KABEERDOSS *et al.*, 2021; ESPOSITO; PRINICPI, 2021).

All patients in our study had laboratory evidence of inflammation (CRP>29 mg/L) at the time of diagnosis. All patients had anemia and elevated D-dimer values (>1200ng/mL). Hypoalbuminemia, lymphopenia, hyponatremia, thrombocytopenia, and increased triglycerides have also been common findings in our study.

Eight (89%) of the patients received antibiotics empirically. The use of empiric antibiotics is indicated until bacterial infection can be ruled out (FERNANDEZ-SARMIENTO *et al.*, 2021; ESPOSITO; PRINICPI, 2021; NAKRA *et al.*, 2020). All of our patients received immunoglobulin and/or corticosteroids, associated with enoxaparin or aspirin. Treatment recommendations suggest IVIG and/or high doses of

corticosteroid as first line of treatment (KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021; KABEERDOSS *et al.*, 2021; ESPOSITO; PRINICPI, 2021; NAKRA *et al.*, 2020). Anakinra, tocilizumab or infliximab could be used in specific cases refractory to treatment with IVIG and methylprednisolone (FERNANDEZ-SARMIENTO *et al.*, 2021; KABEERDOSS *et al.*, 2021; ESPOSITO; PRINICPI, 2021; NAKRA *et al.*, 2020). The use of aspirin is recommended for patients with complete or incomplete Kawasaki disease characteristics (FERNANDEZ-SARMIENTO *et al.*, 2021; ESPOSITO; PRINICPI, 2021; NAKRA *et al.*, 2020). The decision on the use of prophylactic anticoagulation is individualized and based on risk factors and age, and it is recommended for patients with severe left ventricular dysfunction or patients with coronary artery aneurysm (FERNANDEZ-SARMIENTO *et al.*, 2021; ESPOSITO; PRINICPI, 2021). No patients in our study received antiviral therapy or biologic agents. All cases progressed well, and most were discharged from the hospital within 10 days. Only one child remained hospitalized for almost 30 days for adjustment of oral anticoagulation.

Despite the severity of the condition and the fact that many patients require PICU, the median hospital stay for children in the literature is around 7 days and the mortality described in most studies is low, up to 2% (FELDSTEIN *et al.*, 2020; KAUSHIK *et al.*, 2020; (FERNANDEZ-SARMIENTO *et al.*, 2021; KABEERDOSS *et al.*, 2021). A study that described 64 patients North African ethnicity with MIS-C reported a mortality rate of 9%, but in this case series 70% of the children had hypotension and shock (MAHMOUD *et al.*, 2021). This situation is very different from our small sample, because only one of our patients had a shock refractory to volume expansion. As a recent disease, long-term prognostic descriptions are lacking, but studies describe improvement in inflammatory markers and cardiac abnormalities in most patients [9]. Guidelines have recommended follow-up of patients after discharge (FELDSTEIN *et al.*, 2020; KAUSHIK *et al.*, 2020; FERNANDEZ-SARMIENTO *et al.*, 2021; KABEERDOSS *et al.*, 2021; ESPOSITO; PRINICPI, 2021; NAKRA *et al.*, 2020).

5. CONCLUSION

MIS-C is a new syndrome that can affect children of any age, with a still unknown pathogenesis. At this time of pandemic, it should be remembered as a diagnostic hypothesis in any child with persistent fever and multisystem symptoms, or in children with symptoms compatible with Kawasaki disease. Some patients may have a severe clinical picture, associated with shock, gastrointestinal and respiratory symptoms. The children described in our study were mainly schoolchildren, boys and with few comorbidities. All had good evolution with supportive treatment and use of corticosteroids and immunoglobulin. As cardiac involvement is common, cardiac evaluation is recommended for all patients and follow-up after discharge.

Further studies are needed to assess treatment options and long-term prognosis.

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