Multisystem Inflammatory Syndrome in Children Associated with COVID-19 in a Tertiary Level Hospital in Portugal

Síndrome Inflamatória Multissistémica em Crianças Associada a COVID-19 num Hospital de Nível III em Portugal

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a rare and severe manifestation of coronavirus disease 2019 (COVID-19). The aim of this study was to describe the characteristics of children with MIS-C admitted to a pediatric tertiary hospital in Portugal.

Material and Methods: Observational descriptive study of MIS-C patients admitted between April 2020 and April 2021. Demographic and clinical characteristics, diagnostic tests, and treatment data were collected. The diagnosis of MIS-C was based on the World Health Organization and Centers for Disease Control and Prevention criteria.

Results: We reported 45 children with MIS-C. The median age was seven years (IQR 4 - 10 years) and 60.0% were previously healthy. SARS-CoV-2 infection was confirmed in 77.8% by RT-PCR or antibody testing for SARS-CoV-2, and in 73.3%, an epidemiological link was confirmed. All the patients had a fever and organ system involvement: hematologic (100%), cardiovascular (97.8%), gastrointestinal (97.8%), mucocutaneous (86.7%), respiratory (26.7%), neurologic (15.6%), and renal (13.3%) system. Neurological ($p = 0.035$) and respiratory ($p = 0.035$) involvement were observed in patients with a more severe presentation. There was a significant difference of medians when comparing disease severity groups, namely in the values of hemoglobin ($p = 0.015$), lymphocytes ($p = 0.030$), D-dimer ($p = 0.019$), albumin ($p < 0.001$), NT-proBNP ($p = 0.005$), ferritin ($p = 0.048$), CRP ($p = 0.006$), procalcitonin ($p = 0.005$) and IL-6 ($p = 0.002$). From the total number of children, 93.3% received intravenous immunoglobulin, 91.1% methylprednisolone, and one patient (2.2%) received anakinra. Thirteen patients (28.8%) required intensive care and there were no deaths. Of the 21 patients evaluated, 90.4% had reduction of exercise capacity and of the 15 patients who underwent cardiac magnetic resonance, 53.3% had sequelae of cardiac injury.

Conclusion: We observed a large spectrum of disease presentation in a group of patients where most were previously healthy. A small percentage of patients (28.9%) had a severe presentation of the disease. MIS-C is a challenge in current clinical practice and its diagnosis requires a high level of clinical suspicion as the timely initiation of therapy is essential to prevent complications. However, there is no scientific consensus on the treatment and follow-up of these patients.

Keywords: Child; COVID-19/complications; SARS-CoV-2; Systemic Inflammatory Response Syndrome

RESUMO

Introdução: A síndrome inflamatória multissistémica em crianças (MIS-C) é uma manifestação rara, mas grave da doença por coronavírus 2019 (COVID-19). Este estudo teve como objetivo descrever as características de crianças com MIS-C internadas num hospital pediátrico terciário em Portugal.

Material e Métodos: Estudo observacional e descritivo de doentes com MIS-C internados de abril de 2020 a abril de 2021. Analisaram-se dados demográficos, clínicos, exames de diagnóstico e terapêutica. O diagnóstico baseou-se nos critérios da Organização Mundial de Saúde e Centers for Disease Control and Prevention.

Resultados: Foram identificadas 45 crianças, com mediana de idades de sete anos (AIQ 4 - 10 anos) sendo 60,0% previamente saudáveis. A infeção por SARS-CoV-2 foi confirmada por RT-PCR ou serologia em 77,8% dos doentes e 73,3% tinham *link* epidemiológico. Todos os casos cursaram com febre e envolvimento multiorgânico: hematológico (100%), cardiovascular (97,8%), gastrointestinal (97,8%), mucocutâneo (86,7%), respiratório (26,7%), neurológico (15,6%) e renal (13,3%). O envolvimento neurológico ($p = 0,035$) e respiratório ($p = 0,035$) ocorreu nos doentes mais graves. Houve uma diferença significativa das medianas quando comparados grupos de gravidade da doença, nomeadamente nos valores de hemoglobina ($p = 0,015$), linfócitos ($p = 0,030$), D-dímeros ($p = 0,019$), albumina ($p < 0,001$), NT-proBNP ($p = 0,005$), ferritina ($p = 0,048$), pCr ($p = 0,006$), procalcitonina ($p = 0,005$) e IL-6 ($p = 0,002$). Destas crianças, 93,3% realizaram imunoglobulina intravenosa, 91% metilprednisolona e um (2,2%) realizou anakinra. Treze doentes (28,8%) necessitaram de cuidados intensivos e não se registaram óbitos. Dos 21 doentes avaliados seis meses após a alta, 90,4% apresentaram diminuição da tolerância ao esforço e 8/15 (53,3%) lesão cardíaca persistente.

Conclusão: Observámos um amplo espectro de apresentação da doença num grupo de doentes previamente saudável, na sua maioria. Uma pequena percentagem de pacientes (28,9%) teve uma apresentação grave da doença. O diagnóstico da MIS-C é um desafio na prática clínica atual e requer um elevado nível de suspeição pois o início atempado de terapêutica é fundamental para prevenir complicações. No entanto, não existe ainda consenso científico sobre a melhor terapêutica e seguimento destes doentes.

Palavras-chave: COVID-19/complications; Criança; SARS-CoV-2; Síndrome de Resposta Inflamatória Sistémica

INTRODUCTION

In December 2019, an outbreak of pneumonia emerged in the city of Wuhan, China.[1] The new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified on January 3rd, 2020 and

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was responsible for the coronavirus-disease 2019 (COVID-19).[1,2] A pandemic was declared on the 11th of March 2020.[1] The first case of COVID-19 in Portugal was confirmed on the 2nd of March, 2020, and the first pediatric case was confirmed on the 7th March, 2020.[3]

The COVID-19 pandemic has caused substantial morbidity and mortality worldwide, although the number of infected children and those with severe disease is significantly lower when compared to adults. However, in April 2020 in the United Kingdom, a cluster of healthy children with a previous SARS-CoV-2 infection presented with severe disease, hyperinflammatory shock, and features that overlapped with those of toxic shock syndrome and atypical Kawasaki disease (KD).[4,5] The Royal College of Paediatrics and Child Health referred to this condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).[6] This was followed by another report with features resembling not only KD but also secondary hemophagocytic lymphohistiocytosis and macrophage activation syndrome.[4,7,8] The United States Centers for Disease Control and Prevention (CDC), on the 14th May 2020, called this spectrum of COVID-19 in the pediatric population multisystem inflammatory syndrome in children (MIS-C) and introduced a case definition that was reproduced by the World Health Organization (WHO).[9,10]

On the 3rd May, 2021, a total of 3742 confirmed cases and 35 deaths due to MIS-C were reported in the United States of America.[11] Some estimates indicate that MIS-C occurs in two out of 100 000 individuals under 21 years old,[12] but the incidence is unknown, and it appears to be a rare complication of SARS-CoV-2 infection.[12]

MIS-C is characterized, according to the WHO and CDC criteria, by fever, multisystem involvement, and elevated inflammatory markers (Table 1), and it also includes evidence of a SARS-CoV-2 infection and no other microbial cause or alternative plausible diagnosis.[9,10]

The pathogenesis of MIS-C, although not well understood, is thought to be a postinfectious immune-mediated phenomenon, as seen from a time interval of four to six weeks between the occurrence of a peak incidence of COVID-19 cases in communities and MIS-C cases.[7,13-15] A postinfectious phenomenon related with IgG antibody-mediated enhancement of disease is also supported by reports of a higher prevalence of positive tests for SARS-CoV-2 antibodies rather than for positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (rRT-PCR).[16] The prognosis of MIS-C is uncertain because long-term follow-up data are limited.[17] We aim to describe the characteristics of children with MIS-C admitted to a pediatric tertiary hospital in Portugal.

MATERIAL AND METHODS

A case series descriptive study of pediatric patients, under the age of 18 years old, admitted to a pediatric

Table 1 – Case definitions for multisystem inflammatory syndrome in children from the World Health Organization and Centers for Disease Control and Prevention[9,10]

	WHO - World Health Organization	CDC - Centers for Disease Control and Prevention
Age	0 - 19 years of age	< 21 years
Fever	Fever for ≥ 3 days	Fever > 38.0°C for ≥ 24 hours or report of subjective fever lasting ≥ 24 hours
Multisystem involvement	At least 2 clinical signs of multisystem involvement: 1. Rash, bilateral non purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP) 4. Evidence of coagulopathy (prolonged PT, elevated D-dimers) 5. Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)	Clinically severe illness requiring hospitalization Multisystem involvement (2 or more organ system involved): 1. Cardiovascular (e.g., shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrythmia) 2. Respiratory (e.g., pneumonia, ARDS, pulmonary embolism) 3. Renal (e.g., AKI, renal failure) 4. Neurologic (e.g., seizure, stroke, aseptic meningitis) 5. Hematologic (e.g., coagulopathy) 6. Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding) 7. Dermatologic (e.g., erythroderma, mucositis, another rash)
Inflammation markers	Elevated markers of inflammation (e.g., elevated, CRP, ESR or procalcitonin)	Laboratory evidence of inflammation (including, but not limited to ≥ 1 of the following): elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, neutrophilia, lymphocytopenia, hypoalbuminemia
Exclusion of other diagnosis	No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal toxic shock syndromes.	No alternative plausible diagnosis
Evidence of SARS-CoV-2 infection	Any of the following: positive SARS-CoV-2 RT-PCR, positive serology, antigen test, contact with an individual with COVID-19	Any of the following: Positive SARS-CoV-2 RT-PCR, positive serology, positive antigen test, COVID-19 exposure within the 4 weeks prior to the onset of symptoms

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; BNP: brain natriuretic peptide; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; LDH: lactic dehydrogenase; PCT: procalcitonin; PT: pro-thrombin time; RT-PCR: real time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

tertiary level hospital in Portugal from April 2020 to April 2021, with MIS-C. MIS-C diagnosis was based on the WHO and CDC criteria (Table 1). The demographic data, underlying medical conditions, clinical findings and evolution, laboratory results, imaging findings, treatment, complications, and sequelae were analyzed.

We defined MIS-C severity as mild (minimal organ lesion), moderate (moderate to severe organ lesion and need of oxygen support), and critical (severe organ lesion with organ dysfunction or need of inotropic support).

The statistical analysis was performed using the Statistical Package for Social Sciences version 26 (IBM Corp., Armonk, NY, USA) software package. Prior to the statistical analysis, variables were assessed in terms of their normality (visual assessment) and all the variables were found to be non-normally distributed. The Clopper-Pearson exact 95% confidence interval (CI) was calculated for the prevalence of MIS-C in hospitalized patients with a SARS-CoV-2 infection. Continuous variables were expressed as medians and interquartile ranges (IQR) or ranges, and categorical variables were expressed as counts and percentages. Kruskal Wallis and Dunn's multiple comparison tests were used to test for the differences in continuous variables across groups of categorical ones. Bonferroni-adjusted significance tests for pairwise comparisons were used. Fisher's exact test was used to study associations between categorical variables, after disregarding chi-square test due to more than 20% cells with expected count less than 5. A *p* value under 0.05 was considered statistically significant. Patients were not directly studied, and their informed consent was not deemed necessary because the data collected was retrospective and immediately anonymized. Analysis was based on retrospective data collection without any identification of patients thus not requiring specific ethics committee approval.

RESULTS

Of the 312 patients hospitalized with a SARS-CoV-2 infection, 45 had MIS-C (14.4%), which is a prevalence rate of MIS-C in hospitalized patients with SARS-CoV-2 infection of 14.4% (CI 10.7, 18.8). The first case was reported on the 23rd April 2020. The median age was seven years (IQR 4 - 10 years), 31 (68.9%) children were male, and eight (17.8%) were of African ancestry. Twenty-seven (60.0%) were previously healthy (defined as patients without chronic disease as collected from the medical history), and 18 (40.0%) had a chronic disease: obesity (9/45), asthma (4/45), kidney disease (2/45), congenital heart defect (1/45), long gap esophageal atresia (1/45), and epilepsy (1/45).

Twenty-four (53.3%) patients had a history of a previous SARS-CoV-2 infection, 30 (66.7%) reported contact with a sick household member and three (6.7%) with children in school with a confirmed SARS-CoV-2 infection by rRT-PCR. The median duration from contact with a patient with positive rRT-PCR SARS-CoV-2 to the patient's symptom onset was 33 days (range 16 - 60 days, IQR 27 – 44 days).

At the time of MIS-C diagnosis, 35 patients (77.8%) had laboratory evidence of a SARS-CoV-2 infection: 21 patients (46.6%) had positive SARS-CoV-2 antibodies, two patients (2.2%) had positive SARS-CoV-2 rRT-PCR, and 12 patients (26.7%) had both rRT-PCR and antibodies for SARS-CoV-2. Of the 10 patients (22.2%) without laboratory evidence of a SARS-CoV-2 infection, all of them reported an epidemiological context with COVID-19 exposure.

The most common symptoms at hospital admission were fever (45/45, 100%), followed by abdominal pain (27/45, 60%), vomiting (24/45, 53.3%), rash (22/45, 48.9%), and bilateral conjunctival hyperemia (13/45, 28.9%). The median duration from symptom onset to hospital admission was six days (range 2 - 15 days, IQR 4 - 8 days). The clinical

Table 2 – Clinical characteristics of patients according to SARS-CoV-2 rRT and SARS-CoV-2 antibodies

	Total of patients (n = 45)	**Positive SARS-CoV-2 rRT PCR** (n = 14)	**Positive SARS-CoV-2 antibodies** (n = 33)
Fever	45/45 (100%)	14/14 (100%)	33/33 (100%)
Hypotension	12/45 (26.7%)	4/14 (8.9%)	11/33 (33.3%)
Abdominal pain	37/45 (82.2%)	11/14 (78.6%)	29/33 (87.9%)
Vomiting	32/45 (71.1%)	10/14 (71.4%)	23/33 (69.7%)
Diarrhea	14/45 (31.1%)	6/14 (16.7%)	11/33 (33.3%)
Cutaneous rash	34/45 (75.6%)	10/14 (71.4%)	25/33 (75.8%)
Bilateral conjunctival hyperemia	28/45 (62.2%)	9/14 (64.3%)	21/33 (63.6%)
Enanthema	12/45 (26.7%)	4/14 (28.6%)	10/33 (30.3%)
Dyspnea	8/45 (17.8%)	2/14 (14.3%)	8/33 (24.2%)
Peripheral edema	6/45 (13.3%)	3/14 (21.4%)	4/33 (12.1%)
Cervical lymphadenopathies	5/45 (11.1%)	3/14 (21.4%)	3/33 (9.1%)
Headache	10/45 (22.2%)	3/14 (21.4%)	7/33 (21.2%)
Neck stiffness	3/45 (6.7%)	1/14 (7.1%)	2/33 (6.1%)
Gait imbalance	1/45 (2.2%)	1/14 (7.1%)	1/33 (3.0%)

rRT-PCR: real-time reverse-transcriptase polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

characteristics of patients with positive SARS-CoV-2 rRT-PCR and positive SARS-CoV-2 antibodies are displayed in Table 2.

All patients had at least three organ systems involved. The most common were hematologic (45/45, 100%), cardiovascular (44/45, 97.8%), gastrointestinal (44/45, 97.8%), and mucocutaneous (39/45, 86.7%). Respiratory system involvement occurred in 12/45 (26.7%), nervous system involvement in 7/45 (15.6%), and renal system involvement in 6/45 (13.3%). Neurological involvement (p = 0.035) and respiratory involvement (p = 0.041) were associated with the severity of MIS-C (Table 3). Although renal involvement did not show a statistically significant association with severity, it is possible to state by analyzing the data presented in Table 3 that the percentage of patients with renal involvement increased with the severity of the disease.

Regarding hematologic manifestations, 33 patients (73.3%) had anemia, 21 (46.7%) had lymphocytopenia, 38 (84.4%) had elevated prothrombin time (PT), 29 (64.4%) had elevated fibrinogen, and 45 (100%) had elevated D-dimer. We observed elevated lactic dehydrogenase (LDH) in 30 (66.7%) patients and hypoalbuminemia in 33 (73.3%) patients (Table 4). The Kruskal Wallis test provided evidence of significant difference between median peak values in at least one pair of disease severity groups in hemoglobin (p = 0.015), lymphocytes (p = 0.030), D-dimer (p = 0.019) and albumin (p < 0.001). Regarding the median minimum value of hemoglobin there was a significant difference between moderate and critical MIS-C (p = 0.011), in minimum value of lymphocytes (p = 0.030) and maximum value of D-dimer (p = 0.026) significant differences between mild and critical MIS-C, in minimum value of albumin significant differences between mild and critical MIS-C (p = 0.011) and moderate and critical MIS-C (p = 0.002) (Table 5).

Forty-four patients (97.8%) had elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and 20 patients (44.4%) had elevated troponin I levels (Table 4). As for cardiovascular involvement, nine patients (20.0%) needed vasoactive support. There was a significant difference in the medians of maximum peak values of NT-proBNP between groups of disease severity (p = 0.005), with medians in both mild and critical MIS-C (p = 0.025) and moderate and critical MIS-C (p = 0.018) having significant differences (Table 5).

The ECG showed sinus bradycardia in two patients (4.4%) and a first-degree atrioventricular block in one patient (2.2%). Six patients (13.3%) had echocardiographic evidence of perivascular echogenicity of coronary arteries and two patients (4.4%) had evidence of coronary artery aneurysms. We also observed mitral regurgitation (11/45, 24.4%), tricuspid regurgitation (3/45, 6.7%), left ventricular disfunction (4/45, 8.9%), pericardial effusion (5/45, 11.1%), and a patient who had a congenital heart defect had overlap abnormalities compared with the imaging test performed before the MIS-C diagnosis.

We observed ascites in 15 patients (33.3%), mesenteric adenitis in 11 (24.4%), inflammation of the appendix in five (11.1%), ileitis in three (6.7%), colitis in two (4.4%), hepatomegaly in seven (15.6%), splenomegaly in five (11.1%), and gallbladder wall thickening in three (6.7%). Three patients (6.7%) underwent an appendicectomy due to an early presentation with appendicitis.

Mucocutaneous manifestations were present in 39 children (86.7%) with a spectrum of manifestations including cutaneous rash, petechiae, bilateral conjunctival hyperemia, mucositis, cheilitis, and desquamation of the fingers and toes.

Eleven patients (24.4%) had pneumonia identified in a radiography, and 10 patients (22.2%) had evidence of pleural effusion. Respiratory failure occurred in nine patients (20.0%), with one patient needing invasive mechanical ventilation.

Neurological involvement was observed in seven patients (15.6%) and was characterized by headache (2/45,

Table 3 – MIS-C patient severity and patient's characterization

	Total of patients (n = 45)	**Mild MIS-C** (n = 3)	**Moderate MIS-C** (n = 29)	**Critical MIS-C** (n = 13)	***p*-value**
Male	31/45 (68.9%)	2/3 (66.7%)	20/29 (69.0%)	9/13 (69.2%)	1.000[a]
African ancestry	8/45 (17.8%)	0/3 (0%)	5/29 (17.2%)	3/13 (23.1%)	0.828[a]
Obesity	9/45 (20.0%)	0/3 (0%)	7/29 (24.1%)	2/13 (15.4%)	0.847[a]
Positive PCR SARS-CoV-2	14/45 (31.1%)	0/3 (0%)	10/29 (34.5%)	4/13 (30.8%)	0.669[a]
Positive SARS-CoV-2 antibodies	33/45 (73.3%)	3/3 (100%)	18/29 (62.1%)	12/13 (92.3%)	0.070[a]
25(OH)D insufficiency or deficiency	32/38 (84.2%)	1/3 (33%)	20/23 (87.0%)	11/12 (91.7%)	0.079[a]
Cardiovascular involvement	44/45 (97.8%)	2/3 (66.7%)	29/29 (100%)	13/13 (100%)	0.067[a]
Gastrointestinal involvement	44/45 (97.8%)	3/3 (100%)	29/29 (100%)	12/13 (92.3%)	0.356[a]
Hematological involvement	45/45 (100%)	3/3 (100%)	29/29 (100%)	13/13 (100%)	Nd[a]
Mucocutaneous involvement	39/45 (86.7%)	1/3 (33%)	26/29 (89.7%)	12/13 (92.3%)	0.056[a]
Neurological involvement	7/45 (15.6%)	0/3 (0%)	2/29 (6.9%)	5/13 (38.5%)	0.035[a]
Renal involvement	6/45 (13.3%)	0/3 (0%)	2/29 (6.9%)	4/13 (30.8%)	0.091[a]
Respiratory involvement	12/45 (26.7%)	0/3 (0%)	5/29 (17.2%)	7/13 (53.8%)	0.041[a]

[a]: Fischer's exact test. 25(OH)D: serum 25-hydroxyvitamin D; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 4 – MIS-C patient severity and abnormal laboratory values

	Total of patients no, %	Mild MIS-C (n = 3)	Moderate MIS-C (n = 29)	Critical MIS-C (n = 13)
Hb < 11 g/dL	33/45 (73.3%)	3/3 (100%)	18/29 (62.1%)	12/13 (92.3%)
Lymphocytes < 1000 cells/µ	21/45 (46.7%)	0/3 (0%)	12/29 (41.4%)	9/13 (69.2%)
PT > 13 sec	38/45 (84.4%)	3/3 (100%)	26/29 (89.7%)	9/13 (69.3%)
Fibrinogen > 5.0 g/L	29/45 (64.4%)	0/3 (0%)	19/29 (65.5%)	9/13 (69.2%)
D-dimer > 230 µg/L	45/45 (100%)	3/3 (100%)	29/29 (100%)	13/13 (100%)
LDH > 300 U/L	30/45 (66.7%)	2/3 (66.7%)	19/29 (65.6%)	9/13 (69.2%)
Albumin < 38 g/L	33/45 (73.3%)	0/3 (0%)	21/28 (75.0%)	12/13 (92.3%)
CRP > 5 mg/L	45/45 (100%)	3/3 (100%)	29/29 (100%)	13/13 (100%)
Procalcitonin > 0.1 ng/mL	43/45 (95.6%)	2/3 (66.7%)	28/29 (96.6%)	13/13 (100%)
ESR > 11 mm/h	43/43 (100%)	3/3 (100%)	28/28 (100%)	12/12 (100%)
IL-6 > 4 pg/mL	42/43 (97.7%)	3/3 (100%)	26/27 (96.3%)	13/13 (100%)
Ferritin > 79 ng/mL	44/44 (100%)	3/3 (100%)	28/28 (100%)	13/13 (100%)
Amyloid A > 6.5 mg/L	32/33 (97.0%)	3/3 (100%)	19/19 (100%)	10/11 (90.0%)
Troponin I > 35 ng/mL	20/45 (44.4%)	1/3 (33%)	10/29 (34.5%)	9/13 (69.2%)
NT-pro-BNP (superior to higher limit depending with age group[a])	44/45 (97.8%)	3/3 (100%)	28/29 (96.6%)	13/13 (100%)

Laboratory values analyzed were peak values. Thresholds values were obtained from local laboratory reference ranges.
[a]: NT-pro-BNP normal range by age group < 1 month: 263 - 6500 ng/L, < 12 months: 37 - 1000 ng/L, 12 months - 35 months: 39 - 675 ng/L, 3-6 years: 23 - 327 ng/L, 7 - 14 years: 10 - 242 ng/L, 15 - 18 years: 6 - 207 ng/L[37]
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; IL-6: interleukin-6; LDH: lactic dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; PT: pro-thrombin time

4.4%), psychomotor agitation (1/45, 2.2%), meningism (1/45, 2.2%), and bilateral sixth nerve palsy (1/45, 2.2%). Two patients had aseptic meningitis (4.4%) with the cerebrospinal fluid analysis showing pleocytosis with mononuclear cells predominance and mild high cerebrospinal fluid (CSF) protein concentrations. One patient with bilateral sixth nerve palsy had a positive SARS-CoV-2 serology in their cerebrospinal fluid.

Four patients (8.9%) had acute kidney injury, one patient (2.2%) had proteinuria and hematuria, and one patient (2.2%) had orchiepididymitis with a testicular ultrasound presenting enlargement and hypervascularity of both epididymis and spermatic cord enlargement.

An adolescent with an initial diagnosis of a retropharyngeal phlegmon with a cervical adenophlegmon developed clinical (with left ventricular cardiac aneurysms) and laboratory findings that were consistent with MIS-C, an atypical presentation for MIS-C.

All the patients had four or more laboratory biomarkers of inflammation such as elevated C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), serum amyloid A, and ferritin (Table 4) with a tendency for normalization at the time of discharge. Regarding ferritin, although there was evidence of significant difference of median peak value between groups of disease severity ($p = 0.048$), there was no significant difference in a specific pair of groups. There was a significant difference in median maximum values of CRP ($p = 0.006$), procalcitonin ($p = 0.005$) and IL-6 ($p = 0.002$) between groups of disease severity. Significant difference comparing medians both in mild and critical MIS-C and moderate and critical MIS-C was found in CRP ($p = 0.040$, $p = 0.018$), procalcitonin ($p = 0.018$, $p = 0.026$) and IL-6 ($p = 0.004$, $p = 0.033$) (Table 5).

Three patients (6.7%) had minimal organ lesions, 29 patients (64.4%) had moderate to severe organ lesions and the need of oxygen support, and 13 (28.9%) had severe organ lesions with organ dysfunction or the need of inotropic support. Regarding the patients who had a severe phenotype of MIS-C, 13 (81.2%) required intensive care, seven (43.8%) were diagnosed with distributive shock, four (25%) with cardiogenic and distributive shock, nine (56.3%) needed vasoactive support, and one (6.3%) mechanical ventilation due to severe hypoxia. Kawasaki-like phenotype was observed in 18 patients (40.0%), and of those, 14 patients (31.1%) presented an incomplete Kawasaki-like phenotype.

In three patients with the mildest form of the syndrome, an expectant attitude was taken with good clinical evolution. Forty-two patients (93.3%) received intravenous immunoglobulin (2 g/kg single dose or 1 g/kg for two days if hemodynamic instability). Methylprednisolone therapy was administered to 41 patients (91.1%): 35 patients (77.8%) at 2 mg/kg/day and six patients (13.3%) at 10 - 30 mg/kg/day. Higher doses of methylprednisolone were used in patients with a severe presentation of MIS-C, as the therapeutic failure of first-line drugs occurred. Two patients treated with corticosteroids developed hypertension. One patient (2.2%) with severe MIS-C experienced the failure of the first line treatment, and for that reason, received anakinra as a second line therapy.

Forty-three patients (95%) received empirical broad spectrum antibiotics, most of them (33/45, 73.3%) with ceftriaxone and clindamycin. The other therapeutic agents

Table 5 – MIS-C patient severity and peak value during hospitalization

	Median values (interquartile range)				**Kruskal Wallis test**		**Dunn's multiple comparisons tests**		
	Total of patients	Mild MIS-C	Moderate MIS-C	Critical MIS-C	Test value	*p* value	Mild – Moderate MIS-C	Mild – Critical MIS-C	Moderate – Critical MIS-C
Hb g/dL*	10.40 (9.30 - 11.40)	10.4	10.8	9.2	8.426	0.015	1.000	0.700	0.011
Lymphocytes cells/µ*	1000.00 (620.00 - 1585.00)	2910	1000	800	6.996	0.030	0.173	0.030	0.408
PT sec[a]	15.00 (13.90 – 16.25)	14.1	15.6	14.1	3.820	0.148	N/a	N/a	N/a
Fibrinogen g/L*	5.40 (4.45 – 6.30)	4.7	5.5	5.8	2.041	0.360	N/a	N/a	N/a
D-dimer µg/L[a]	944.00 (572.00 – 1993.50)	531	920	1741	7.895	0.019	0.244	0.026	0.183
LDH U/L[a]	340.0 (293.50 – 407.50)	355	317	344	0.071	0.965	N/a	N/a	N/a
Albumin g/L*	29.90 (25.00 – 37.50)	40.4	33.1	25	15.413	< 0.001	0.445	0.011	0.002
CRP mg/L[a]	197.60 (142.10 – 292.75)	121.1	169.9	295.9	10.093	0.006	0.813	0.040	0.018
Procalcitonin ng/Ml[a]	1.54 (0.67 – 4.83)	0.42	1.35	3.78	10.640	0.005	0.434	0.018	0.026
ESR mm/h[a]	71.00 (59.00 – 81.00)	75	68.5	74	1.335	0.513	N/a	N/a	N/a
IL-6 pg/mL[a]	105.9 (45.20 – 415.00)	8.12	62	415	12.356	0.002	0.159	0.004	0.033
Ferritin ng/mL[a]	418.50 (262.15 – 889.68)	276.7	378.9	689	6.057	0.048	0.306	0.056	0.382
Amyloid A mg/L[a]	714.00 (409.00 – 1235.00)	246	714	940	0.796	0.672	N/a	N/a	N/a
Troponin I ng/mL[a]	28.00 (2.40 – 260.65)	38	12.1	149	5.057	0.080	N/a	N/a	N/a
NT-pro-BNP ng/L[a]	2970.00 (1518.50 – 7738.00)	354.5	2241	9576	10.672	0.005	0.600	0.025	0.018

*: peak value regarding the minimum value during hospitalization, [a]: peak value regarding the maximum value during hospitalization.
N/a: Dunn's multiple comparisons test is not performed as the entire test does not show significant differences between samples;
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; IL-6: interleukin-6; LDH: lactic dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; PT: pro-thrombin time.

included enoxaparin (prophylactic doses) in 17 patients (37.8%), acetylsalicylic acid in 22 patients (48.9%), and gastric protection in 42 (93.3%). Vitamin D supplementation was administered to 32 patients (71.1%): 18 (40%) with vitamin D deficiency and 14 (31.1%) with insufficiency.

Cytomegalovirus reactivation was observed in one patient. One patient presented macrophage activation syndrome, toxicoderma, and disseminated herpes simplex virus type 1 infection and received valacyclovir, two cycles of methylprednisolone therapy (one at 30 mg/kg/day and other at 10 mg/kg/day), and second line immunosuppression treatment with anakinra with a good outcome.

Significant weight loss (defined as at least 10% weight loss) associated with MIS-C was observed in five patients (11.1%), median weight loss 8.4% (IQR 5.95 - 14.55%).

Patients were discharged with a median length of stay of nine days (range 3 - 28 days, IQR 7.00 - 12.50 days) and there were no fatalities.

All the children underwent outpatient follow-up (minimum eight months - to date, all patients still have follow-up appointments) and performed multidisciplinary evaluations (infectious diseases, cardiology, physical and rehabilitation medicine, nutrition, and psychology). Thirty-two of the 44 patients (72.7%) with cardiac involvement underwent an echocardiogram two to eight weeks after discharge: 30 (30/32, 93.7%) had a normal echocardiogram and two (2/32, 6.3%) presented coronary artery abnormalities and these patients belonged to the group of patients with coronary abnormalities diagnosed during hospitalization. Fifteen of the 44 patients (15/44, 34.1%) underwent cardiac magnetic resonance imaging (MRI) because of systolic dysfunction or cardiac injury in the acute period and eight (8/15, 53.3%) presented myocardial fibrosis. Of those, four patients (4/15, 26.7%) presented subacute myocarditis, two (2/15 13.3%) subacute pericarditis, one (1/15, 6.7%) coronary artery ectasia, and one (1/15, 6.7%) left ventricle dilatation.

Seven patients with respiratory involvement (7/12, 58.3%) performed pulmonary function tests and one patient (1/7, 14.3%) revealed abnormal diffusion and another patient (1/7, 14.3%) showed abnormal resistance.

Five patients who had renal system involvement (5/6, 83.3%), performed a renal scintigraphy that showed renal scars in three (3/5, 60%) and a subacute lesion in one (1/5, 20%).

Twenty-one patients (21/45, 46.7%) were evaluated by physical and rehabilitation medicine. The referral criteria to physical and rehabilitation medicine were based on the patients' or parents' complaints of the change in functional capacity or functional decline. Regarding these patients, 12/21 (57.1%) were referred for cardiopulmonary deconditioning and 3/21 (14.3%) had a decrease of autonomy with the inability to independently perform the activities of daily living that they could before the diagnosis. Nineteen patients (19/21, 90.4%) presented a reduction in exercise capacity and, therefore, benefited from a rehabilitation program: seven (7/19, 36.8%) in an outpatient treatment program and 12 (12/19, 63.2%) in a home-based self-controlled exercise program.

A nutritional assessment was also performed in 7/45 patients (15.6%) and three (3/7, 42.8%) were referred to obesity outpatient follow-up, while four (4/7, 57.1%) received instructions on how to improve their nutritional health.

Five patients (5/45, 11.1%) were psychologically assessed, and of those, two were referred to child and adolescent psychiatry. The referral criteria for a psychological assessment were based on the patients' or parents' complaints of anxiety and depressive symptoms related with hospital isolation, an acute period of serious illness, and in some cases, serious sequelae.

DISCUSSION

MIS-C is a severe condition associated with a SARS-CoV-2 infection and evidence is still needed to clarify the various aspects of this syndrome. Our case series focused on describing the clinical presentation and short-term outcomes of this syndrome.

As in previous reports, we found a similar median age (seven years), slight predominance of male patients (68.9%), and most of the patients were previously healthy (68.9%).[14,18-21] Some reports showed that obesity may be a risk factor for MIS-C, but in our case, obesity did not have a statistical association with the severe phenotype of MIS-C.[22]

Current evidence supports a temporal association between a SARS-CoV-2 infection and MIS-C, with MIS-C typically occurring within two to four weeks after an infection or the peak of COVID-19 cases in communities, which is consistent with our case series in which we observed an interval of 33 days from contact with a patient with positive rRT-PCR SARS-CoV-2 to the patient's symptom onset.[7,12,14,19] The high percentage of seropositivity for SARS-CoV-2 with MIS-C, as seen in this case series and other published studies, also supports the hypothesis of MIS-C being a post-infectious presentation of COVID-19 in children.[15,23] Given that a large subset of SARS-CoV-2-infected children display mild to no symptoms, some children may develop MIS-C with little to no advance warning, and in some cases, caregivers may not even be aware that the child was previously infected with SARS-CoV-2.[24]

In our case series, the median duration from symptom onset to hospital admission was six days, a long period of time considering the potential severity of disease. These data allow us to conclude that this syndrome is not always recognized given the possibility of milder presentation but in any case, this syndrome has potentially serious consequences and should motivate close monitoring and hospitalization. To obviate long periods until hospitalization and the management of these patients, it is important to emphasize the importance of a high clinical suspicion of MIS-C in children. In addition, the use of a panel of laboratory tests for inflammation, hypercoagulability, and organ damage might assist in the early identification and management of MIS-C. However, there are no clear data indicating the predictive value for each clinical symptom or laboratory value in diagnosing MIS-C.[25]

Fever and gastrointestinal symptoms, such as diarrhea and abdominal pain, were predominant in the clinical presentation of MIS-C as in other series.[14,15,20] Gastrointestinal manifestations, sometimes mimicking appendicitis or even inflammatory bowel disease were reported to be one of the main presenting clinical features in children with an MIS-C diagnosis.[21,26,27] In agreement with previous reports, we reported three patients in this case series who underwent an appendicectomy following a diagnosis of appendicitis. Differentiating acute appendicitis from abdominal symptoms due to MIS-C may be difficult given the overlap of symptoms but imaging findings and laboratory evaluations could indicate a diagnosis of MIS-C.

Cardiac involvement in previous reports included 71% to 100% of patients and may include an unusual cardiac injury shown by high concentrations of troponin and brain natriuretic peptide, left ventricular dysfunction, coronary artery dilation or coronary artery aneurysm, and electrical conduction abnormalities.[4,7,13-15,20] In this case series, we observed highly elevated troponin and NT-proBNP. In addition, elevated IL-6 levels might also be due to stretched cardiomyocytes and cardiac fibroblasts along with macrophage activation, as these immune cells are the main producers of IL-6.[13] For this reason, cardiac involvement is a hallmark in this syndrome, as observed in our series.[4,7,12,14,18,20,22,28,29] This highlights the importance of monitoring cardiac involvement. Although most patients have markers of cardiac injury, the echocardiogram may not show abnormalities that only a cardiac MRI may identify regarding whether it is an acute injury or cardiac sequelae.

Neurological involvement is reported in other case series, and it is described in up to 20% of affected patients, with varying severity, from irritability and meningismus to severe encephalopathy, which is concordant with our results in which we reported neurological involvement in 15.6% of patients.[30] In addition, we also found that neurological involvement was associated with the severity of MIS-C.

Previous studies reported that a group of patients with MIS-C had a higher incidence of respiratory symptoms and severe respiratory involvement, often requiring intensive care treatment and higher case fatality rates, thereby also satisfying the MIS-C criteria.[31,32] In fact, we observed that respiratory involvement was also associated with the severity of MIS-C in our series.

Regarding management and therapeutic agents, a stepwise approach to immunomodulatory treatment in MIS-C is recommended, but there are insufficient data to compare the efficacy of IVIG and glucocorticoids in MIS-C.[25] We reported 13 patients with severe MIS-C, and of those, six needed methylprednisolone pulses and one anakinra as the second line therapy, as there was therapeutic failure of the first-line drugs.

As also recommended by the literature, all the patients were admitted for observation while the diagnostic evaluation was conducted.[25] Since there were other possible etiological diagnoses, such as malignancy or inflammatory conditions, all the patients underwent additional diagnostic studies and received broad-spectrum antibiotics during hospitalization, until a diagnosis was established, and negative culture results were available.

Because of the high inflammatory state and thrombotic risk based on D-dimer elevation in MIS-C, anticoagulant therapy such as low-molecular-weight heparin (LMWH) is commonly used in these cases.[14,29,33] According to our unit's guidelines, we initiated enoxaparin in prophylactic doses in 17 patients (37.8%) which included patients with severe presentation, prolonged immobilization, and patients with D-dimer elevation that was six-fold the upper limit. Acetylsalicylic acid is also recommended, particularly in MIS-C patients with Kawasaki-like phenotype, coronary artery aneurysms, and thrombocytosis.[25] Also based on our unit's guidelines, we initiated acetylsalicylic acid in anti-platelet doses in 22 patients (48.9%), which included patients who complied with the aforementioned recommendations. Finally, as for vitamin D, it can reduce the risk of infections through several mechanisms such as inducing pathways to lower viral replication rates, reducing concentrations of pro-inflammatory cytokines, and increasing concentrations of anti-inflammatory cytokines.[34] For this reason, evaluation of the vitamin D status has been recommended and correction suggested, and so it is useful to measure the baseline level of serum 25-hydroxyvitamin D at hospital admission.[34] However, further research is needed in this area to confirm the role of vitamin D in MIS-C.[34]

Previous studies showed a mortality rate of 1.7% - 1.8% in MIS-C patients.[21,31] Fortunately, in our case series, there were no deaths. The long-term outcomes of MIS-C remain unknown, but close follow-up is essential given the paucity of knowledge about this syndrome as well as the potential for morbidity gains. Acute cardiac findings are postulated to be a result of cardiac stunning rather than progressive endovascular changes observed in similar conditions, such as Kawasaki disease.[17] Nevertheless, in our case series, eight patients showed abnormalities in the cardiac MRIs and most likely will require long-term treatment. The risk of long-term cardiovascular complications and the approach to monitoring is extrapolated from the follow-up studies of children with Kawasaki disease and viral myocarditis since there is limited data on the post-discharge follow-up of patients with MIS-C. A cardiac MRI may be indicated three to six months after MIS-C diagnosis, especially in patients who presented with moderate-severe left ventricle dysfunction.[35] The usual practice is to limit physical activity for a period until cardiac function fully recovers, which is similar to the practice for children recovering from myocarditis.[36]

Other sequelae following discharge include muscular weakness, reduced exercise capacity, anxiety, and depressive symptoms. Longer-term follow-up will help define the extended natural history of MIS-C.[17] The remarkable reduction in functional exercise capacity in our patients should be attributed to various factors such as the underlying inflammatory nature of the disease, a pre-illness sedentary lifestyle, and the side effects of high-dose corticosteroid use. These factors are in addition to the lack of

physical activity opportunities for all young people during the COVID-19 pandemic.

MIS-C is still characterized by the scarcity of information regarding its etiology, pathophysiology, and long-term outcomes which impairs the optimal management of these patients. Furthermore, this syndrome represents potentially severe medical sequelae which, despite its rarity, enhances not only the importance of additional research but also of COVID-19 mitigation efforts to prevent the transmission of SARS-CoV-2 and, consequently, MIS-C.[24]

The early identification of MIS-C is essential for a timely approach to the disease, and for that reason, studies comparing MIS-C patients to other patients hospitalized with SARS-CoV-2 will be useful in identifying the possible predictors for the early diagnosis of MIS-C.

There are other questions about MIS-C that remain unanswered including management and optimal treatment, which disclose the importance of future randomized clinical trials and of reporting this syndrome globally to provide better care for patients.

CONCLUSION

We observed a large spectrum of disease presentation, and most patients were previously healthy. A small percentage of patients (28.9%) had a severe presentation of the disease. Nonetheless, even those patients had a good short-term outcome since we did not report any deaths in our case series. Despite that, the long-term outcomes could be an important burden on children's health. In fact, we observed several cardiac, physical, and psychological sequelae, and for that reason, it is important to emphasize that these patients should have a long follow-up with a particular focus on cardiac involvement since it is a hallmark in MIS-C.

AUTHOR CONTRIBUTIONS

JVM, RV: Data collection, analysis, and interpretation; draft of the paper; critical review of the paper.

AMG, TS, CG: Data analysis and interpretation; review of the paper.

MJB: Data analysis and interpretation; critical review of the paper.

All the authors read and approved the final manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

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