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Pediatric Multisystem Inflammatory Syndrome (MIS-C) associated with Covid-19 culminating in multiple complications: A case report

Síndrome Inflamatória Multissistêmica Pediátrica (SIM-P) associada à Covid-19 culminando com múltiplas complicações: Um relato de caso

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ABSTRACT

On January 30, 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern, due to the novel coronavirus 2019 (definitively named on February 12, 2020 as COVID-19). Initially, Covid-19 infection did not appear to affect the paediatric population, with few reported cases, negligible morbidity, and mortality, and generally asymptomatic. However, subsequently, the English National Health System (NHS) issued an alert about new clinical manifestations of COVID-19 in children, which may be temporarily linked to a previous SARS-CoV-2 infection and determined by history of exposure, serology, or viral detection by RT-PCR, described as a paediatric multisystem inflammatory syndrome temporally associated with SARS-COV-2 (MIS-C). This paper reports the case of a 3-year-old and 6-month-old male patient, neuropathic, microcephalic, epileptic who sought medical attention with persistent fever and abdominal pain. Laboratory tests showed myositis, hepatitis, pancreatitis, positive PCR, elevated D-dimer and serology for covid-19 with non-reactive IgM and reactive IgG, thus meeting the diagnostic criteria for MIS-C. As for its prognosis, MIS-C is a dangerous and potentially fatal disease. The estimated mortality rate for MIS-C is between 0% and 5.3%, which is considered low but much higher than the overall mortality rate for children with COVID-19 (0.09%). Treatment depends on the severity of the disease, the risk of complications, and the possibility of follow-up, with most patients requiring hospitalization.

Keywords: Pediatric Multisystem Inflammatory Syndrome, Coronavirus, Inflammation, Paediatrics.

1 INTRODUCTION

In 2020, a new coronavirus emerged that can cause potentially serious respiratory illness in some people, mainly affecting adults over the age of 60 and people with comorbidities. On 30 January 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (1).

Coronaviruses are RNA viruses that affect humans, other mammals, and birds. As of 2019, six different types of coronaviruses have been identified as causing human disease, most of which are associated with colds and mild upper respiratory tract infections in immunocompetent patients of all age groups. Of these, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) strains stand out, which have been associated with severe and potentially fatal cases with respiratory failure. A seventh strain was identified in 2019, the novel coronavirus 2019 (definitively named on February 12, 2020 as COVID-19), identified in the city of Wuhan, Hubei province (1).

Initially, Covid-19 infection did not appear to affect the paediatric population, with few reported cases, negligible morbidity and mortality, and generally asymptomatic. When respiratory symptoms appeared, they were mild, and there were more records of gastrointestinal symptoms in children than in adults (2, 3).

The spread of COVID-19 appears to occur primarily through contact with an infected person, through respiratory droplets from coughing, sneezing, or droplets of saliva or nasal secretions. Diagnostic confirmation is performed by real-time polymerase chain reaction (RT-PCR) and genome sequencing techniques (1).

On April 7, 2020, the first 6-month-old child with COVID-19-associated Kawasaki Disease (KD) was reported in the United States. After April, cases emerged in Europe, North America, and Latin America. In July, Brazil reported its first cases, most of which resulted in severe morbidity and mortality, requiring hospitalization and intensive care unit (ICU) care. The English National Health Service (NHS) has issued an alert about new clinical manifestations of COVID-19 in children, which may be temporarily linked to a previous SARS-CoV-2 infection and determined by history of exposure, serology, or viral detection by RT-PCR, described as a paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (MIS-C) (4, 5, 6).

This condition can have features similar to complete or incomplete KD, toxic shock syndrome, and macrophage activation syndrome, involving multiple organs, including the heart, gastrointestinal tract, skin, and eyes, most common in schoolchildren and adolescents. In Brazil, as of February 2021, the Ministry of Health had recorded 736 cases and 46 deaths in children and adolescents associated with MIS-C. The most affected age group is between 0 and 4 years old and is mainly male (6, 7).

2 CASE REPORT

Patient, 3 years and 6 months old, male, with previous diagnosis of Hypoxic-Ischemic Neuropathy, microcephaly and epilepsy since 2 months of age after meconium Aspiration Syndrome and congenital cytomegalovirus was questioned.

The patient attended the pediatric emergency room of the city of origin with a history of inconsolable crying, increased airway secretion, hyporexia and fever for three days (38.4°C - 39.5°C). On physical examination, the patient presented irritated, with strong crying and pain facies, which worsened on abdominal palpation, which differed from her baseline neurological alteration.

In the initial evaluation, imaging and laboratory tests were performed, and there was no abnormality in the chest and abdomen X-ray, as well as computed tomography (CT) of the abdomen and pelvis. Laboratory investigation revealed leukocytosis with rod, increased lactic dehydrogenase, creatine phosphokinase and liver enzymes, thus diagnosed with myositis and hepatitis.

The patient was admitted to the hospital and empirically initiated broad-spectrum antibiotic therapy due to persistent fever, volume expansion, analgesia, and the entire protocol for the condition in question. With no evident improvement in pain and fever, the laboratory investigation was expanded, with an increase in lipase, diagnosed with pancreatitis, and a positive PCR was also noted, as shown in Table 1.

After three days of hospitalization, the patient developed re-entrant seizures in the presence of fever, accompanied by drops in saturation and the need for supplemental oxygen, and it was decided to transfer him to the Pediatric Intensive Care Unit (ICU). A CT scan of the head, cerebrospinal fluid collection, and several serology tests were performed, all with normal results. RT-PCR for SARS-COV-2 was collected with a non-reactive result, but with serology for Covid-19 with non-reactive IgM and reactive IgG.

After the serology result, in addition to the clinical picture, the case was reported as suspected MIS-C and new tests were collected for diagnostic complementation and investigation of possible complications associated with the condition. After the results, as shown in Table 1, it was seen that the patient met the diagnostic criteria for MIS-C due to having, in addition to serology for Covid-19 with positive IgG, persistent fever, abdominal pain, myositis, hepatitis, pancreatitis, positive PCR, and elevated D-dimer. Following the investigation protocol, an echocardiogram was performed and no abnormalities were identified. The patient progressed with clinical improvement despite treatment with symptomatic patients (morphine, antipyretics) and antibiotic therapy (ceftriaxone for 10 days).

Table 1

Exams/Days	**Admission**	**D1**	**D2**	**D3**	**Loud**
Hemoglobin	11,6	12,0	10,2	10,3	9,7
Leukocytes	33300	12100	8690	13900	16000
Rods	11%	4%	2%	6%	3%
Platelets	153000	102000	153000	237000	260000
PCR	Negative	Negative	12	Negative	Negative
Urea	12	10	18	16	10
Creatinine	0,47	0,49	0,32	0,51	0,30
RNI	---	1,08	1,17	---	1,0
AST/TOTAL	140/25	---	180/30	---	50/12
FAL/GGT	458/390	---	404/460	---	264/269
BT/BD/BI	---	0,2/0,1/0,1	---	---	---
Triglycerides	46	---	---	123	---
Albumina	4,6	---	---	---	---
CPK	4128	4793	1193	1958	271
CK-MB	---	---	---	180	---
DHL	1537	2060	1720	1902	687
Amylase	---	---	---	61	23
Lipase	---	---	---	424	62
Ferritin	---	---	---	---	---
D-dimer	---	---	---	654	---

Legend: D: Day; CRP: C-reactive protein; RN1: International normalized ratio; AST: Aspartan transaminase; ALT: Alanine aminotransferase; FAL: Alkaline phosphatase; GGT: Gamma Glutamyl Transferase; BT: Total bilirubins; BD: Direct bilirubin; BI: Indirect bilirubin; CPK: Creatine phosphokinase; CK-MB: Creatine kinase fraction MB; DHL: Lactic Dehydrogenase

3 DISCUSSION

Although possible mechanisms have been proposed, the pathophysiology of MIS-C has yet to be fully elucidated. Theoretically, MIS-C can be caused by: a) direct effects of the SARS-CoV-2 virus; b) immune dysregulation after SARS-CoV-2 infection; (c) a combination of both mechanisms (6).

In clinical practice, we observed that even patients with MIS-C behave differently, reinforcing the notion that the syndrome is a spectrum with distinct clinical presentations. The

likelihood of developing a more severe form in children with mild presentations is not well established (6).

In an analysis of 345 cases, the most prevalent comorbidities were: asthma, neurological disorders, diabetes, obesity, cardiovascular disease, and malignant/hematological diseases (3). The patient mentioned in this study had hypoxic-ischemic neuropathy, microcephaly and epilepsy, reinforcing this finding.

The diagnosis of MIS-C is established according to the criteria proposed by the Ministry of Health, based on the PAHO/WHO case definition (WHO/2019-nCoV/MIS_Children_CRF/2020.2),5 validated by the Brazilian Society of Pediatrics, the Brazilian Society of Rheumatology, the Brazilian Society of Cardiology, and the Evandro Chagas Institute, described below (Chart 1) (5, 8):

Table 1

DEFINITION
Cases who were hospitalized with: • Presence of high (> 38°C) and persistent (≥ 3 days) fever in children and adolescents (up to 19 years of age) And • At least two of the following signs and/or symptoms: - Nonpurulent 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 elevation of troponin, or N-terminal B-type natriuretic peptide (NT-proBNP)], - Evidence of coagulopathy (due to elevated PT, aPTT, or D-dimer). - Acute gastrointestinal manifestations (diarrhoea, vomiting or abdominal pain). And • Elevated inflammation markers (ESR, CRP or procalcitonin, among others). And • Rule out any other causes of infectious and inflammatory origin, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. And • Evidence of COVID-19 (positive molecular biology, antigen or serological test) or history of contact with a COVID-19 case. Additional Comments • Children and adolescents who meet full or partial criteria for Kawasaki syndrome or toxic shock syndrome may be included. • Healthcare providers should consider the possibility of MIS-C in any characteristic pediatric death with evidence of SARS-CoV-2 infection.

Legend: PT - prothrombin time, aPTT - activated partial thromboplastin time, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein.

Laboratory tests usually show lymphopenia, neutropenia, anemia, thrombocytopenia, and elevated markers of inflammation (CRP, ESR, and ferritin). Patients may experience increases in markers of cardiac, liver, and kidney damage due to end-organ involvement. Among imaging tests, echocardiography is essential in MIS-C because cardiac involvement is common and helps differentiate severe acute illness from COVID-19 (2, 4, 9). Among the acute manifestations of the

disease, pericardial effusion and myocarditis with altered left ventricular ejection fraction are the most common alterations on echocardiography (4).

MIS-C is a dangerous and potentially fatal disease. The estimated mortality rate for MIS-C is between 0% and 5.3%, which is considered low but much higher than the overall mortality rate for children with COVID-19 (0.09%). Treatment depends on the severity of the disease, the risk of complications, and the possibility of follow-up, with most patients requiring hospitalization. We recommend hospitalization for all patients with suspected MIS-C, even for observation, performance, and pairing of laboratory tests due to the potential severity of the disease and the fact that these patients are not always warranted in an outpatient visit (6, 10).

Initial treatment of moderate to severe cases of MIS-C includes administration of immunoglobulin, corticosteroids, and acetylsalicylic acid (ASA). Other interventions depend on clinical presentation and response to initial therapy (10). In the case presented, the patient showed improvement only with the use of symptomatic patients and antibiotics, not requiring other therapies suggested in the literature, evolving with significant clinical improvement and without complications.

4 CONCLUSION

Covid-19 infection is still recent, as is MIS-C, which has a temporal association with previous SARS-CoV-2 infection. The fact that MIS-C is a spectrum with different clinical presentations makes the diagnosis difficult, directly interfering with the appropriate treatment and correct notification of real cases, and may cause underreporting of the disease. Thus, it is extremely important to provide guidance to health professionals about the existence of MIS-C and its diagnostic criteria to change this reality. Further studies are still needed to elucidate its pathophysiology, patient evolution, and possible long-term sequelae.

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