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## Letter to the editor

# COVID-19 in children: a case report of Multisystem Inflammatory Syndrome (MIS-C) in São Paulo, Brazil



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Dear Editor,

As COVID-19 continues to spread in Brazil and other countries, the impact of the disease among children, initially considered less important,<sup>1</sup> will increasingly be more relevant. The role of children in viral transmission and its impact in epidemic expansion, as well as the extent of the diversity of clinical presentation, are still unclear. At the end of April, the United Kingdom South Thames Retrieval Service alerted on a new clinical picture manifesting as a hyper-inflammatory syndrome, with multi-organ involvement similar to Kawasaki Disease and with potential evolution to a shock syndrome. This represented a new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection.<sup>2</sup> This Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2 infection occurs weeks after infection and may evolve unnoticed.<sup>3</sup> This is how-

ever a new and potentially life threatening condition that many pediatricians may not be aware.

Herein we report a case of SARS-CoV-2 related MIS-C observed at end of April 2020. A previously healthy 10-year-old male child was admitted to the pediatric department with a seven-day history of fever, abdominal pain and diarrhea. There was no history of contact to a COVID-19 patient or symptomatic acquaintances. On physical examination, he was afebrile, dehydrated, prostrated and with conjunctival erythema. On the following day the patient had high fever (39.6°C), which persisted at a lower level (37.8–38°C) until the seventh day. Laboratory tests showed anemia (hemoglobin of 10.4 mg/L and hematocrit of 35.7%), 14,600 leukocytes/mm<sup>3</sup> (90% polymorphonuclear) but with only 730 (5%) lymphocytes/mm<sup>3</sup>. Hypoxemia, with a saturation of 93.5% with arterial blood gas of pO<sub>2</sub> of 63 mmHg and pCO<sub>2</sub> of 29 mmHg, bicarbonate of 20 mmol/L, BE: -2.3 mmol/L

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were documented along with a chest tomography showing ground-glass opacities in less than 25% of the lungs, small bilateral pleural effusion and of abdominal tomography with enlargement of the lymph nodes, measuring up to 2.6 cm. The electrocardiogram was normal. On the fourth day of hospitalization, the patient showed high levels of inflammatory markers, including a C-reactive protein (CRP) of 176 mg/L and D-dimer of 2564 ng/mL associated high ferritin (533 ng/mL), fibrinogen (620 mg/dL) and hypoalbuminemia (2.4 g/dL), with normal lactic acid, creatinine, AST, ALT, CPK and CK-MB. The chest radiography showed increased cardiac area. After five days chest tomography showed consolidation in the left lower lobe lung with air bronchogram associated with some loss of lobe volume suggesting atelectasis. Minimal bilateral basal pleural thickening, with significant pleural effusion on the right and moderate on the left was observed, and a slight increase in the cardiac area suggestive of pericardial effusion, with a large amount of free fluid in the abdominal cavity (ascites). Nasopharyngeal swabs at admission and on the 8th day of hospitalization, processed at the service reference laboratory did not detect SARS CoV-2 or Influenza (A and B) RNA. On the 6th day of hospitalization D-dimer levels were higher (5000 ng/mL) with CRP of 140 mg/L. Autoantibodies tests were negative (anti-neutrophil cytoplasm — ANCA, anti-cardiolipin IgM and anti-SM antibodies) as was the serology to HIV and Hepatitis B/C.

Since admission, the patient received ceftriaxone for 10 days concomitantly with oseltamivir for five days and macrolide from the 3rd day of hospitalization (4 days of clarithromycin followed by four days of azithromycin). On the 4th day of hospitalization, with hemoglobin of 9.8 g/dL and hematocrit of 33.1%, he received red cell concentrate. Albumin and furosemide were used on the 4, 5, 8 and 10th day of hospitalization. Three doses of hydroxychloroquine were administered. On the ninth day of hospitalization, the echocardiogram was normal, the level of albuminemia was 3.4 g/dL and CRP was 37 mg/L.

In spite of only supportive measures, the child evolved with resolution of ascites, pleural and pericardium effusion, normalization of laboratory tests, being discharged on the 14th day of hospitalization and was asymptomatic at last observation two months thereafter. Plasma from venous blood collected at discharge was stored at  $-80^{\circ}\text{C}$  and subsequently tested for COVID-19, that was reagent in all tests used, four rapid tests; positive (IgG/IgM) in Wondfo<sup>®</sup> and IgG positive and IgM negative in three (Vazyme<sup>®</sup>, Clungene<sup>®</sup> and Livzon<sup>®</sup>). Moreover, patient's serum showed a cutoff index of 129, at the Roche Elecsys<sup>®</sup> anti-SARS-CoV-2 assay. Family members, all asymptomatic, tested negative on Wondfo<sup>®</sup>.

At the time of diagnosis, this was one of the first MIS-C cases in Brazil, but now the Brazilian Ministry of Health (BMH) have a surveillance program for the syndrome, with 194 cases reported by August 23. The reported mortality among these 194 cases is 7.1%, higher than the 1.5% (12/783) reported in a recent literature review.<sup>4</sup> Fever and abdominal pain are common manifestations of the syndrome<sup>3</sup> that usually present also with hypotension and cardiac dysfunction<sup>6</sup> that were not outstanding in this child. However, multi-organ involvement, the confirmed SARS-CoV-2 serological tests and laboratory alterations including lymphopenia and inflammatory mark-

ers, hallmarks of the syndrome, support the diagnosis, that fulfill the CDC, BMH and WHO criteria for MIS-C.<sup>3,5,13</sup> The case definition of MIS-C is extremely broad and may not be specific enough<sup>6</sup> but is useful and may be improved as more information is obtained. As the virus spreads, the presence of antibodies to the virus will become more prevalent, and documenting past COVID-19 infection with serology may not be so helpful, but today this is the only indication for the clinical use of a serological test.<sup>7,12</sup> Thus, although serologic testing help establish a diagnosis when patient present with late complications of COVID-19 illness, such as MIS-C, both clinical and laboratory criteria need to be improved.

The lack of viral RNA detection is not impediment for the diagnosis,<sup>3,5</sup> as the syndrome may occur after viral clearance from upper airways and false negative results are not uncommon. Antibodies appear 1–2 weeks after infection. In primary infections, IgM responses typically develops first, eventually waning and with IgG response dominating thereafter. Thus, high levels of IgG in the absence of IgM may suggest a time of weeks or even months from infection.<sup>7</sup> However, different kinetics of antibody appearance has been described in COVID-19 cases, with atypical antibodies kinetics, and a longer persistence of IgM may occur.<sup>8</sup>

Age and clinical features are characteristic of the initial descriptions of MIS-C in the literature, while fever, shock, abdominal pain, vomiting and diarrhea are common presenting features.<sup>9</sup> Kawasaki Disease (KD) shares some common features with MIS-C, but Asian children have the highest incidence KD<sup>6</sup> whereas MIS-C seems rare in this population.<sup>1,6</sup> Moreover, KD occurs mostly in children less than five years of age, with a peak incidence at 10 month of age.<sup>6</sup> In a prospective observational study with 21 children and adolescents admitted with features of Kawasaki-like disease over a 15-day period, during the COVID-19 pandemic in Paris, France, 12 (57%) had African ancestry.<sup>10</sup>

This child recovered with only supportive care, no longer requiring intensive care after a few days and showing complete recovery. Although a severe illness, with 68% requiring intensive care,<sup>4</sup> few deaths have been reported in other countries, often resulting from complications related to therapeutic intervention.<sup>6</sup> This is an important point to be observed when exploratory therapy is considered. Children have been treated with anti-inflammatory treatment, including par-enteral immunoglobulin and steroids<sup>3,11</sup> and a few received TNF-alfa inhibitors, IL-1 and IL-6 receptor antagonists.<sup>3</sup> However, a better understanding of the pathogenic mechanism of the disease may help defining the appropriate interventions for specific cases. Although some authors have described MIS-C as a type of cytokine storm, important differences from the prototype antibody chimeric reactions, observed with some monoclonal therapeutic agents, have been highlighted,<sup>11</sup> and different immunopathogenic mechanisms may be expected. Moreover, high serum IL-6 is also common in some systemic juvenile arthritis<sup>6</sup> and the role of cytokines and other features of MIS-C still lack proper understanding to guide therapy. There is also an urgent need to standardize data describing clinical presentations, severity, outcomes and epidemiology.<sup>13</sup>

Clinical features suggestive of this syndrome should prompt alertness among primary care, emergency units and

pediatricians during the expected expansion of COVID-19 in Brazil and in other countries.

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### Conflicts of interest

The author declares no conflicts of interest.

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### REFERENCES

- Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* 2020;109:1088-95.
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395:1607-8.
- Ministério da Saúde. Boletim Epidemiológico, vol. 51; 2020. No. 35. <https://www.saude.gov.br/images/pdf/2020/September/04/Boletim-epidemiologico-SVS-35-editado.pdf>. [Accessed 7 September 2020].
- Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr Respir Rev.* 2020, <http://dx.doi.org/10.1016/j.prrv.2020.08.001>. Aug 11:S1526-0542(20)30117-2.
- Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). <https://www.cdc.gov/mis-c/hcp/index.html>. [Accessed 15 July 2020].
- Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol.* 2020:1-2.
- Perez-Toledo M, Faustini SE, Jossi SE, et al. Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with paediatric inflammatory multi-system syndrome. *MedRxiv.* 2020, <http://dx.doi.org/10.1101/2020.06.05.20123117>, 2020.06.05.20123117. Published 2020 Jun 7. Preprint.
- Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med.* 2020;26:845-8.
- Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health.* 2020;4(9):669-77, [http://dx.doi.org/10.1016/S2352-4642\(20\)30215-7](http://dx.doi.org/10.1016/S2352-4642(20)30215-7) [published correction appears in *Lancet Child Adolesc Health.* 2020 Jul 17].
- Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ.* 2020;369:m2094.
- Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. *J Exp Med.* 2020;217:e20200678.
- CDC. <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html>, 2020,. [Accessed 15 July 2020].
- WHO. <https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>, 2020,. [Accessed 16 July 2020].