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Diagnosis of pediatric multisystemic inflammatory syndrome associated with COVID-19

Diagnóstico del síndrome inflamatorio pediátrico multisistémico pediátrico asociado con COVID-19

Diagnóstico da síndrome inflamatória multissistêmica pediátrica associada à COVID-19

ABSTRACT
SARS-CoV-2 may have caused an increase in cases of Pediatric Multisystem Inflammatory Syndrome (P-SIM), causing shock and organ failure. The aim of the article was to elucidate what to evaluate to diagnose SIM-P associated with COVID-19. Method: Literature review on the Evidence Aid and Pubmed platform with the descriptors: pediatric multisystem inflammatory syndrome and COVID-19. 89 articles were found, selecting 26 after screening. Two epidemiological bulletins and a post from the Society of Pediatrics of São Paulo were manually added. Results: The epidemiological aspects, the presence of fever, skin rash and gastrointestinal and cardiac alterations, help to characterize the syndrome. Laboratory tests show an increase in: C-reactive protein, D-dimer, procalcitonin, serum ferritin, fibrinogen and cardiac markers. Conclusion: The identification of alterations is crucial for the differential and correct diagnosis of P-SIM. Furthermore, the standardization of data collection and the identification and description of signs and symptoms would cooperate for the diagnosis.
DESCRIPTORS: Infantile Onset Multisystem Inflammatory Disease; Diagnosis; COVID-19.

RESUMEN
El SARS-CoV-2 puede haber causado un aumento en los casos de Síndrome Inflamatorio Multisistémico Pediátrico (P-SIM), causando shock e insuficiencia orgánica. El objetivo del artículo fue dilucidar qué evaluar para diagnosticar SIM-P asociado con COVID-19. Método: Revisión de la literatura en la plataforma Evidence Aid y Pubmed con los descriptores: síndrome inflamatorio multisistémico pediátrico y COVID-19. Se encontraron 89 artículos, seleccionando 26 después del cribado. Se agregaron manualmente dos boletíns epidemiológicos y una publicación de la Sociedad de Pediatría de São Paulo. Resultados: Los aspectos epidemiológicos, la presencia de fiebre, erupción cutánea y alteraciones gastrointestinales y cardíacas, ayudan a caracterizar el síndrome. Las pruebas de laboratorio muestran un aumento de: proteína C reactiva, dímero D, procalcitonina, ferritina sérica, fibrinógeno y marcadores cardíacos. Conclusión: La identificación de alteraciones es crucial para el diagnóstico diferencial y correcto de SIM-P. Además, la estandarización de la recopilación de datos y la identificación y descripción de signos y síntomas cooperarían para el diagnóstico.
DESCRIPTORES: Enfermedad Inflamatoria Multisistémica de Inicio en la Infancia; diagnóstico; COVID-19.

RESUMO
O SARS-CoV-2 pode ter provocado um aumento dos casos da Síndrome Inflamatória Multissistêmica Pediátrica (SIM-P), causando choque e falência de órgãos. O objetivo do artigo foi elucidar o que avaliar para diagnosticar a SIM-P associada à COVID-19. Método: Revisão bibliográfica na plataforma Evidence Aid e Pubmed com os descritores: pediatric multisystem inflammatory syndrome e COVID-19. Encontrou-se 89 artigos, selecionando 26 após triagem. Adicionou-se, manualmente, 2 boletins epidemiológicos e 1 postagem da Sociedade de Pediatria de São Paulo. Resultados: Os aspectos epidemiológicos, a presença de febre, rash cutâneo e alterações gastrointestinais e cardíacas, ajudam a caracterizar a síndrome. Nos exames laboratoriais são encontrados aumento de: proteína C-reativa, D-dímero, procalcitonina, ferritina sérica, fibrinogênio e marcadores cardíacos. Conclusão: A identificação das alterações é crucial para o diagnóstico diferencial e correto da SIM-P. Ademais, a padronização da coleta de dados e a identificação e descrição dos sinais e sintomas cooperaria para o diagnóstico.
DESCRITORES: Doença Multissistêmica Inflamatória de Início na Infância; diagnóstico; COVID-19.

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INTRODUCTION

SARS-CoV-2 caused 3,69 million deaths as of June 3rd, 2021, [1] being children, a small portion of confirmed cases (2-7,8%)[2], usually asymptomatic. [2-10] Inflammatory diseases in this group increased 4 to 6 weeks after the peak of COVID-19, [2,11] therefore, the National Health Service of the United Kingdom declared an alert for Pediatric Multisystem Inflammatory Syndrome (P-SIM). [2] In November 2020 it was reported in 7 countries [11] an increase in P-SIM cases after the acute stage of infection. [2] In Brazil, until September 2020, there were 380 cases in children up to 19 years of age and 26 deaths, 13 of which in children aged 0-4 years (37,4% of cases). [12] It is estimated that PIMS mortality is 2%, with high rates of supportive therapy for multiple organs. [13]

The P-MIS, of unclear pathophysiology, [5,6,9,14] has been described as a variant, with clinical features similar to Kawasaki (KS) and toxic shock (TSS) syndromes, [2-5,8-12,15-17] among other infections. [14] Thus, PIMS-TS is also referred to as atypical or incomplete KS and P-MIS temporarily associated with SARS-CoV-2 (PIMS-TS). [2] As PIMS is similar to other diseases and has a poor prognosis, it is important to identify changes that favor its correct diagnosis, in order to guide a more appropriate treatment and follow-up. [5,8] The aim of the article was to elucidate what must be evaluated to diagnose SIMP-TS.

METHOD

An integrative review was performed on June 3, 2021, with a search on the Evidence Aid platform, with the descriptor pediatric multisystem inflammatory syndrome, and on Pubmed, with the descriptors pediatric multisystem inflammatory syndrome and COVID-19, with the free full text filters, studies in humans, in English and Portuguese, and books and documents were excluded. Inclusion criteria: articles on PIMS published from 2019 onwards. Exclusion criteria: no approach to diagnosis and focus on other similar syndromes. A screening was performed, based on Prisma (2009), with application of the inclusion and exclusion criteria. 86 results were found in the Pubmed platform, being selected, respectively, 33 for the title, 26 for the abstract and 21 for the reading of the full article. In the Evidence Aid platform, 3 articles were found, 1 repeated article being eliminated and 2 selected by title, abstract and reading of the full article, respectively. Two epidemiological bulletins and a post from the Society of Pediatrics of São Paulo were added manually.

For the construction of the article, the data were analyzed by 4 authors and condensed by 2, taking into account the objective and application of the inclusion and exclusion criteria. Data were organized according to clinical, laboratory and examination diagnosis, in order to facilitate later comparison.

RESULTS

23 articles were used for the construction of the article, 17 from 2020 and 6 from 2021, 2 epidemiological bulletins, one from the World Health Organization and the other from the Ministry of Health; and a post from the Society of Pediatrics of São Paulo. The main results of the chosen articles are presented below (Table 1).

Table 1. Main results of selected articles.

TITLE	AUTHORS/ YEAR	MAIN RESULTS
COVID-19 and multisystem inflammatory syndrome in children and adolescents	Jiang, L. et al./20202	Symptoms and pathophysiology of PIMS are similar to Kawasaki disease (KD), toxic shock syndrome, and macrophage activation syndromes. There is still no accepted protocol over PIMS.

Oral manifestations of COVID-2019-relatede multisystem inflammatory syndrome in children: a review of 47 pediatric patients	Halepas, S. et al./20203	Of the 47 patients with PIMS: 100% had fever, 57,5% conjunctivitis, 68,1% systemic rash, 12,8% extremity edema, 19,2% cervical lymphadenopathy, 48,9% red or swollen lips and 10,6% documented strawberry tongue. Furthermore, 38,3% had diarrhea, 51,1%% vomiting, 14,9% cough, 14,9% irritability and 6,4% rhinorrhea. Most patients had elevated CRP (93,6%), ESR (87,5%) and D-dimer (93,5%).
SARS-CoV-2 infections with emphasis on pediatric patients: a narrative review	Yamamoto, L. et al./20204	Studies have reported that children with PIMS develop more bowel symptoms and less severe conditions.
Characteristics of pedriatric multi-system inflammatory syndrome (PMIS) associated with COVID-19: a meta-analysis and insights into pathogenesis	Zou H. et al./20205	Analysis of 23 articles, with 182 patients with PIMS. The main symptoms were persistent fever (80%), gastrointestinal symptoms (90%), shock (74%), left ventricular dysfunction (70%), DK criteria (17%) and respiratory symptoms (9%). Elevated C-reactive protein, IL-6, troponin and NT-pro BNP and reduced albumin and lymphocytes were found.
Multisystem inflammatory syndrome associated with COVID-19 from the pediatric emergency physician's point of view	Simon J. H. et al./20206	The clinical features of PIMS and DK are similar. In these there are nonspecific symptoms, such as: abdominal pain, diarrhea, vomiting, conjunctivitis, skin rash and cervical adenopathy. It was found in PIMS: increased CRP, IL-6, erythrocyte sedimentation rate, procalcitonin, D-dimer, ferritin, lactic dehydrogenase, fibrinogen, neutrophils; and decreased lymphocytes and/or albumin. ECG: features indicate acute coronary syndrome. Echocardiography: change in contractility.
The importance of heart and brain imaging in children and adolescents with Multisystem Inflammatory Syndrome In Children (MIS-C)	Mavrogeni, S. I. et al./20217	In PIMS, cardiovascular complications are the most common, with an increase in NT-pro BNP, troponin, D-dimer, ferritin, CRP and procalcitonin. ECG with abnormalities in 56%, with AVB in 20%, QTc prolongation in 28% and nonspecific ST alterations in 56%. Echocardiography may show depressed LV function, coronary artery abnormalities, mitral valve regurgitation, and pericardial effusion. Furthermore, mental alterations were described.
A dermatologic perspective on multisystem inflammatory syndrome in children	Naka, F. et al./20208	Gastrointestinal symptoms and fever were the most common. Cutaneous findings were nonspecific maculopapular eruptions, conjunctivitis, urticariforms, livedo reticularis, acral and papulovesicular lesions, petechiae, erythema multiforme, edema in the hands and feet, dry and red lips. PIMS is similar to KD, but mean age, race predilection and some clinical manifestations differ.
Pediatric Inflammatory Multisystem Syndrome Associated With SARS-CoV-2: A Case Series Quantitative Systematic Review	Bustos, B. R. et al./20209	Study with 468 children: 100% febrile, 58% with skin rash, 56% with conjunctivitis, 76% in shock. Elevated inflammation and cardiac damage markers. Chest imaging showed pulmonary infiltrates in 41%, left ventricular dysfunction in 72% on echocardiogram, 24% with abnormalities in the coronary arteries, and 24% with pericarditis or pericardial effusion.
Hematological manifestations of SARS-CoV-2 in children	Kosmeri, C. et al./202010	Hematological manifestations are rare, with lymphopenia in hospitalized older children and lymphocytosis in infants. Anemia and thrombocytopenia were uncommon.
Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations, and management	Kabeerdoss, J. et al./202011	PIMS is triggered by SARS-CoV-2 infection and affects several organs. Many clinical manifestations are similar to KD, but they are different diseases.

Multisystem inflammatory syndrome in children related to COVID-19: An update regarding the presentation of two critically ill patients	Taffarel, P. et al./202113	PIMS is an inflammatory condition with frequent cardiovascular involvement. The exact incidence of the disease is not known, and it is important to carry out studies with a collection of laboratory and imaging tests in order to guide the correct diagnosis.
Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children	Rowley A. H./202014	There is clinical similarity between PIMS and DK, and it is difficult to distinguish both. Even though SARS-Cov-2 has not been proven to cause PIMS, when appearing during outbreaks of COVID-19 in developed countries, the relationship is highly suggestive.
Multisystem inflammatory syndrome in pediatric COVID-19 patients: a meta-analysis	Toraih, E. A. et al./202115	Recently, the connection between COVID-19 infections and DK was investigated. Even though PIMS is rare in COVID-19 positive children, there is a need for aggressive and long-term medical treatment.
Paediatric Inflammatory Multisystem Syndrome Temporally-Associated with SARS-CoV-2 Infection: An Overview	Carter, M.J. et al./202016	Groups of previously healthy children in Europe and the US have been reported to have persistent fever, multisystem inflammation, and pancarditis. Apparently PIMS is a rare complication of asymptomatic SARS-CoV-2 infection in children.
Phenotype, Susceptibility, Autoimmunity, and Immunotherapy Between Kawasaki Disease and Coronavirus Disease-19 Associated Multisystem Inflammatory Syndrome in Children	Chen, M.R. et al./202117	COVID-19 in children is mostly mild, however, a multisystem inflammatory syndrome similar to KD can occur in children, and it is necessary to differentiate the syndromes. The symptoms are similar so you must know how to differentiate the syndromes.
Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: Current knowledge and implications for public health	Raffertu, M.S. et al./202118	PIMS is believed to be associated with previous SARS-CoV-2 infection. Thus, mitigating the transmission of SARS-CoV-2, in addition to preventing COVID-19, presents a likely strategy for preventing PIMS.
The Natural History of Severe Acute Respiratory Syndrome Coronavirus 2–Related Multisystem Inflammatory Syndrome in Children: A Systematic Review	Aronoff, S. C. et al./202019	The clinical manifestations of PIMS, which appears to be a serious complication of SARS-CoV-2 infection, are not well defined. It presents with fever, abdominal pain, vomiting and diarrhea, rash, conjunctival injection, cheilitis, and changes in the extremities.
COVID-19 Associated Multisystem Inflammatory Syndrome: A Systematic Review and Meta-analysis	Baradaran, A. et al./202020	PIMS prevalence increased during the COVID-19 pandemic. In this study, of 600 patients with PIMS associated with COVID-19, there were fever (97%), shock (55%), gastrointestinal symptoms (80%), rash (60%), conjunctivitis (54%) and respiratory symptoms (39%). The clinical picture of PIMS is similar to that of KD.
Vitamin D in Corona Virus Disease 2019 (COVID-19) Related Multisystem Inflammatory Syndrome in Children (MIS-C)	Feketea, G. et al./202121	PIMS is a rare and serious complication of COVID-19. Apparently, vitamin D can reduce the risk of infection and is a possible biomarker.
Multisystem inflammatory syndrome in children: A systematic review	Ahmed, M. et al./202022	A current challenge is the differentiation between patients with PIMS, KD and toxic shock syndrome. The PIMS clinic presents extreme inflammation, fever, abdominal symptoms, conjunctivitis and skin rash, starting three to four weeks after infection by COVID-19, which may progress to shock and cardiorespiratory failure..
A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection	Kaushik, A. et al./202023	PIMS resembles Kawasaki disease, but there are several questions that remain unanswered, including its pathogenesis, long-term complications, and immunity.
Update on the diagnosis and management of COVID-19 in pediatric patients	Cartlotti, A. P. C. P. et al./202025	PIMS, similar to Kawasaki disease, was considered a possible complication of COVID-19.
Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS–CoV-2	Diorio, C. et al./202026	PIMS is a pediatric complication of COVID-19. The distinction between severe COVID-19 and PIMS is made through cytokine profiling and peripheral blood smear examination.

Clinical Diagnosis

SIMP-TS is more common from 7 [2,12,18] to 10 years 18 and in males. [3,11,19,20] As for ethnicity, there is a greater relationship between African, [2,11,18,21] Hispanic [2] and Latino, than white. [11,18]

Among the signs and symptoms, five articles considered shock as dominant [2,5,7,9,15] (68,1%)[15] and two considered cardiovascular alterations, [11,16] (80%) [11], being pericarditis 25 and myocarditis [11,16,23] the most frequent ones. [11,14,25] Coronary abnormalities [1,6,7,9,11] (9[11]-38%[6]) considered most frequent are coronary dilation [5-7,11,20] and small aneurysms. [7,11,18] Arrhythmia was also reported, [2,6,7,18] pericarditis, valve regurgitation [7,19] and pericardial effusion. [3,6,7,19]

Gastrointestinal (GI) manifestations were frequent[2,3,5,7,9-11,15,16,18-23] (70[23]-92%[11]), being reported diarrhea[4,6,11,18,20,22,24] (38,3[3]-52%[6]), abdominal pain[4,6,11-13,20,24] (50[4]-100%1[8]) and vomiting. [11,18,20] (45[6]-68,3%[22]).

The most reported mucocutaneous manifestations (42[8]-74%[11]) were cutaneous rash, [3,4,6-10,12,13,18-20,22,23] conjunctivitis, [6-8,10,18-23] raspberry tongue, red cracked lips, [3,7,8,23] and cheilitis. [3,6,8,24] The respiratory manifestations [11,12,18,19] (50[4]-70%[11]) found were tachypnea, retraction and increased respiratory effort. [19] Dyspnea [18,22] and cough [18,22,23] have also been reported.

The most reported neurological manifestations were headache, [7,11,15,18,20,22,23] meningeal signs, [6,7,11,18,20,23] visual changes, [15,18,20] confusion [7,18,23] and lethargy. [15,22] Other changes: fever, [2-26] hematological changes, (76%) hemodynamic instability (60-80%)[11] and hypotension [19,12,14,15] (68,1[15]-77%[19]). Five articles reported acute kidney injury [5,9,15,19,20]. In relation to multiple organ failure, [11,26] 71% of 115 children had 4 or more organs involved. [11]

Laboratory diagnosis

It is common in patients with PIMS-TS to increase: erythrocyte sedimentation,[3,6,8,10,11,15,21] C-Reactive Protein (CRP), [3,4,5,6,9,11,15-19,22] procalcitonin, [6-7,11,15,17,18,19,21,22] D-dimer, [2,3,6-11,15,18,19,21,23,25,26] fibrinogen [2,6-8,10,14-19,21,23,26] and serum ferritin. [2,6-8,10,15,19,21,23] In addition to the presence of lymphopenia, [5,8-11,13,16] increased liver enzymes [6,11,15,26] and inflammatory markers. [11-18,22,26] Other findings were lymphopenia [4-6] (66-80%[19]), hypoalbuminemia, [5,6,8,15,18,21] thrombocytopenia, [3,7,23,25] neutrophilia, [3,7,8,11,17,21,23,25,26] increased interleukins 1, 8[23], 6[6,8,14,15,21,26] and 10, and tumor necrosis factor. [6,26] Furthermore, there is a cytokine storm [2,4,6,11,14] 2 weeks after infection. [11]

It was reported in 13 articles cardiac injury (80%) [2] with high concentrations of troponin and brain natriuretic peptide (BNP), [2,4-7,10,11,15,19,22-24,26] indicating heart failure and myocardial damage. [11,19,24]

Three articles cited CPR-RT positive for the virus, [19,22,23] with positivity between 32,9[19]-84,7%[22] of patients.

The United Kingdom considers clinical manifestations, organ dysfunction, exclusion of microbial causes and CPR testing as diagnostic criteria. The Centers for Disease Control and Prevention (CDC) assesses: age (<21); signs and symptoms; absence of another more likely diagnosis; signs of severe disease and involvement of more than two organs; and positive test for COVID-19 or exposure of up to 4 weeks to the virus prior to symptoms.

Diagnosis by imaging exams

There have been reports of left ventricular hypokinesia, [23] reduction in left ventricular ejection fraction (LVEF) [2,6,7,9,18-20,23] (5017-73%)[6], unusual dilation, [2,10,18] coronary ectasia [18,19] and aneurysms 2 of frank coronary artery. [19] The electrocardiographic abnormalities (55,3[15]-56%[7]) found were: increased PR interval; [6,11] elevated T wave, depressed 6 or inverted; [6] prolonged QT interval; [6,7] ST segment changed [6,11,16] (56%7) and first-degree atrioventricular block (20%). [7]

Chest radiography [4,15,23] and chest computed tomography showed opacity and infiltrates in 13,7% (90) patients. [23] In addition, 55,8% of pneumonia and/or pleural effusions were found on x-ray. [19]

Criteria used

The United Kingdom considers clinical manifestations, organ dysfunction, exclusion of microbial causes and CPR testing as diagnostic criteria. [2] The Centers for Disease Control and Prevention (CDC) assesses: age (<21); [3,25] signs and symptoms; absence of another more likely diagnosis; signs of severe disease and involvement of more than two organs; and positive test for COVID-19 [2,3,25] or exposure of up to 4 weeks to the virus prior to symptoms. [2,25]

Differential Diagnosis with Kawasaki Syndrome

KS is a vasculitis[2,3,7,11,14,15,17,22,24] and a major cause of childhood acquired heart disease.[2] Some similarities are: cytokine storm;[11] shock; GI symptoms; hypoalbuminemia; and cardiac involvement. [2] However, KS is more common under the age of 5 years[7,11,22,24] and in Northeast Asian children.[11,17,21] In addition, when compared to PIMS-TS, in KS there is severe anemia, [10] lymphadenopathy, presence of cytotoxic T cells,[3] thrombocytosis,[17] lower elevation of inflammatory markers[2,5,17] and cardiac,[5] lower occurrence of neurological complications[7] and GI, coagulopathies,[7,11,14] shock[7,11,17] (<10%[14]), myocarditis [11,17] (<5%) and multiple organ dysfunction.[11] The association between the diseases was considered inconclusive [2,15] and the difficult differential diagnosis.[22]

DISCUSSION

It was observed that PIMS-TS does not have a defined age range, although it predominates in late childhood and extends into adolescence, it affects more males and African ethnicity. The most prevalent symptoms are: fever; skin rash; hemodynamic instability; gastrointestinal changes such as abdominal pain and vomiting; pericarditis and myocarditis. Respiratory symptoms, on the other hand, are less evident, which contributes to the differential diagnosis of COVID-19. The most frequent laboratory and imaging alterations were increased erythrocyte sedimentation, CRP, procalcitonin, D-dimer, troponin, BNP, fibrinogen and serum ferritin, in addition to the presence of lymphopenia and neutrophilia, and reduced LVEF. The diagnostic criteria have not been established and the pathophysiology is still unknown, so the health professional must take into account the aforementioned characteristics, especially those most frequently found to diagnose the syndrome and carry out the treatment and adequate follow-up of the patient.

For the correct diagnosis of PIMS-TS it is necessary to consider: patient's age; persistence of fever; presence of inflammatory markers; signs and symptoms of organ dysfunction; absence of another more likely diagnosis; and temporal relationship with COVID-19 infection or contact with an infected person.

PIMS-TS is very similar to KS and, although the differential diagnosis is considered difficult, differences between them have been found, such as the predominant age group and more expressive symptoms. Therefore, the identification of the alterations found is crucial for the differential and correct diagnosis of PIMS-TS.

As limitations of the study we have: low number of articles; high variety of symptoms analyzed, making it difficult to identify symptoms, as some studies did not report the absence or presence of changes in some systems; and high variety of laboratory alterations and imaging exams, which may be due to the lack of resources and materials available. Thus, there may be an underreporting of symptoms and alterations, mainly due to the difficulty in differentiating PIMS-TS from other syndromes.

CONCLUSION

For the correct diagnosis of PIMS-TS it is necessary to consider: patient's age; persistence of fever; presence of inflammatory markers; signs and symptoms of organ dysfunction; absence of another more likely diagnosis; and temporal relationship with COVID-19 infection or contact with an infected person.

More studies on the association between KS and PIMS-TS are needed, with challenges to be overcome for a better understanding of the disease. ■

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