MULTISISTEMIC PEDIATRIC INFLAMMATORY SYNDROME (PIMS) AND THE ASSOCIATION WITH SARS-COV-2

SÍNDROME INFLAMATÓRIA PEDIÁTRICA MULTISISTÊMICA (PIMS) E A ASSOCIAÇÃO COM A SARS-COV-2

SÍNDROME INFLAMATORIO PEDIÁTRICO MULTISISTÉMICO (PIMS) Y LA ASOCIACIÓN CON SARS-COV-2

Eduardo Haruo UCHIYA[1]

ABSTRACT: Introduction: PIMS means pediatric inflammatory multisystem syndrome. It describes a new health condition seen in children who were infected with new coronaviruses, recovered and later show an immune response that results in significant levels of inflammation in the organ systems and symptoms. Objective: To analyze scientific production on Systemic Pediatric Inflammatory Syndrome (PIMS) in relation to the diagnosis of SARS-CoV-2. Method: The integrative literature review is the method employed for investigation. The following inclusion criteria were adopted: original article in English, available online and in full: year of publication in 2020, in the MEDLINE database, on the PubMed Search Engine. Articles that do not respond to the objective of the study will be excluded. The descriptors applied were: Coronavirus Infections, Syndrome, Child. Results: Five publications were included and categorized in "Scientific production on the correlation of Pediatric Inflammatory Syndrome with SARS-CoV-2". It showed in the main results that in the analysis of the studies, four studies of children diagnosed with COVID-19 (recent or previous, with past history) developed the syndrome, and that one of the authors links SARS-CoV-2 with Kawasaki Disease (DK) with disagreement. Conclusion: SARS-CoV-2 is related to PIMS, regardless of the development of the syndrome, it can generate serious health complications for the child.

KEYWORDS: Coronavirus infections. Syndrome. Child.

RESUMO: *Objetivo: Analisar a produção científica sobre a PIMS associado ao diagnóstico de SARS-CoV-2. Método**:** A revisão integrativa da literatura é o método empregado para a investigação. Foram adotados os seguintes critérios de inclusão: artigo original em inglês, disponível on-line e na íntegra: ano de publicação em 2020, na base de dados MEDLINE, no motor de busca PubMed. Os artigos que não responderem ao objetivo do estudo serão excluídos. Os descritores foram aplicados: Infecções por Coronavírus, Síndrome, Criança. Resultados: Cinco publicações foram incluídas e categorizadas em "Produção científica sobre a correlação da Síndrome inflamatória pediátrica com SARS-CoV-2". Mostrou nos principais resultados que, quatro estudos com crianças diagnosticadas com COVID-19 (recente ou anterior, com história passada) desenvolveram a síndrome e que um dos autores associa SARS-CoV-2 com a doença de Kawasaki. Conclusão: SARS-CoV-2 está relacionado à PIMS, independentemente do desenvolvimento da síndrome, pode gerar sérias complicações de saúde para a criança.*

[1] Americas University Center (FAM), São Paulo – SP – Brazil. Undergraduate student in Nursing. ORCID: https://orcid.org/0000-0003-2942-7641. E-mail: eduardoharuouchiya@hotmail.com

***PALAVRAS-CHAVE**: Infecções por coronavírus. Síndrome. Criança.*

***RESUMEN**: Objetivo: Analizar la producción científica en PIMS asociada con el diagnóstico de SARS-CoV-2. Método: la revisión integradora de la literatura es el método utilizado para la investigación. Se adoptaron los siguientes criterios de inclusión: artículo original en inglés, disponible en línea y completo: año de publicación en 2020, en la base de datos MEDLINE, en el motor de búsqueda PubMed. Se excluirán los artículos que no respondan al objetivo del estudio. Se aplicaron los descriptores: Infecciones por coronavirus, Síndrome, Niño. Resultados: Se incluyeron y clasificaron cinco publicaciones en "Producción científica sobre la correlación del síndrome inflamatorio pediátrico con el SARS-CoV-2". En los resultados principales se mostró que cuatro estudios con niños diagnosticados con COVID-19 (reciente o anterior. Con antecedentes)) desarrollaron el síndrome y que uno de los autores asocia el SARS-CoV-2 con la enfermedad de Kawasaki Conclusión: El SARS-CoV-2 está relacionado con PIMS, independientemente del desarrollo del síndrome, puede generar complicaciones de salud graves para el niño.*

***PALABRAS CLAVE**: Infecciones por coronavirus. Síndrome. Infantil.*

Introduction

Since the beginning of the COVID-19 pandemic, children have been a population relatively untouched by the new corona virus. If infected, children generally had few symptoms, unless an underlying condition compromised their health (CHILDREN'S HOSPITAL LOS ANGELES, 2020).

> Most children with SARS-CoV-2 infection are asymptomatic or have mild symptoms of the infection. To date, children have accounted for a minimal portion of the cases in the global pandemic of COVID-19 and epidemiological data from many countries show that they are a minority among affected patients. Children and adolescents under 18 accounted for only 1.7% of reported cases in the USA, 1% in the Netherlands and 2% of a large observational cohort in the United Kingdom. Studies from several countries have confirmed that serious illness and death from COVID-19 in children are rare, despite the low accuracy of the data due to the absence of true population denominators. However, attention has now increased in relation to children's vulnerability, for two reasons: first, knowledge of the degree to which children transmit COVID-19 is critical to knowing how countries will reopen communities after the lockdown and, secondly, in the last two months, children who have developed a significant systemic inflammatory response have been identified - due to this there are several descriptions of new manifestations of a serious disease, similar to Kawasaki's disease, related to COVID-19 infection, bringing a new facet of this disease (BEREZIN, 2020).[2]

[2] A maioria das crianças com infecção por SARS-CoV-2 é assintomática ou apresenta sintomas leves da infecção. Até o momento, as crianças responderam por uma porção mínima dos casos na pandemia global da COVID-19 e dados epidemiológicos de muitos países mostram que são minoria entre os pacientes afetados. Crianças e

Some children had some or all of the characteristics seen in Kawasaki's disease, a children's disease that can result in enlargement or aneurysm of the coronary arteries. The characteristics observed included fever, rash, conjunctivitis; red and swollen hands; and red and chapped lips. Some children showed clinical and laboratory signs of cytokine storm syndrome, an exaggerated systemic immune response that caused organ damage in adults with COVID-19 (BOSTON CHILDREN'S HOSPITAL, 2020).

PIMS stands for pediatric inflammatory multisystemic syndrome. It describes a new health condition seen in children who were infected with new coronaviruses, recovered and later show an immune response that results in significant levels of inflammation in the organ systems and symptoms. PIMS is similar to other inflammatory conditions, such as Kawasaki disease and toxic shock syndrome. Children who have PIMS generally did not show obvious symptoms when infected with new coronaviruses, such as a cough, and were generally healthy before the development of PIMS (CHILDREN'S HOSPITAL LOS ANGELES, 2020).

Finally, many children had coagulopathies; cardiac dysfunction; diarrhea, bloating and other gastrointestinal symptoms (with some children having positive stool tests for SARS-CoV-2); or acute kidney injury. Respiratory symptoms were not always a prominent feature (BOSTON CHILDREN'S HOSPITAL, 2020).

The information available on PIMS is extremely limited due to the small number of cases compared to the impressive number of people affected by COVID-19 (CHILDREN'S HOSPITAL LOS ANGELES, 2020). In this sense, the present study aims to analyze scientific productions that deal with PIMS in relation to the diagnosis of SARS-CoV-2.

Method

This study uses the bibliographic survey method, from the integrative literature review, which has the function of synthesizing results of previous studies on the proposed subject.

> Integrative reviews have the potential to show a comprehensive understanding of specific issues and to point out existing gaps in knowledge. The steps

adolescentes menores de 18 anos representaram apenas 1,7% dos casos reportados nos EUA, 1% na Holanda e 2% de uma grande coorte observacional no Reino Unido. Estudos de vários países confirmaram que doenças graves e morte por COVID-19 em crianças são raras, apesar de baixa precisão dos dados devido à ausência de verdadeiros denominadores populacionais. Entretanto, agora a atenção aumentou em relação à vulnerabilidade das crianças, por dois motivos: em primeiro lugar, o conhecimento do grau em que as crianças transmitem COVID-19 é fundamental para se saber como os países reabrirão as comunidades após o bloqueio e, em segundo lugar, nos últimos dois meses foram identificadas crianças que desenvolveram uma resposta inflamatória sistêmica significativa - devido a isso estão ocorrendo diversas descrições de novas manifestações de uma doença grave, semelhante à doença de Kawasaki, relacionada à infecção por COVID-19, trazendo uma nova faceta dessa doença (BEREZIN, 2020).

> followed in preparing this review will be: establishing the research question, searching the literature, evaluating data, analyzing the included studies, interpreting the results and presenting the review (SOUZA; SILVA; CARVALHO, 2010).[3]

Data collection was carried out in June 2020, in the Medical Literature Analysis and Retrieval System Online database (MEDLINE), in the search engine of the United States National Library of Medicine (PubMed) and had inclusion criteria, original articles, in English, available online and in full, with year of publication of 2020, and that answer the question: "What is the relationship between COVID-19 and the Pediatric Inflammatory Multisystem Syndrome (PIMS)?"

The Health Descriptors (DeCS) were applied: Coronavirus Infections, Syndrome, Children, as well as their respective versions in English and Spanish.

In order to delimit the research, publications with the main subjects were excluded: Periodic syndrome associated with cryopyrin (CAPS), NLRC4, Meningitis, Human Immunodeficiency Virus (HIV), Eosinophilia, Pediatric sarcoidosis, Type II mucopolysaccharidosis, as it is not the subject of this review.

The identification of the articles was made independently, totaling fifty-four complete articles available. Works such as theses, titles and abstracts that do not correspond to the review proposal were excluded.

From May to June 2020, with a detailed reading of the articles, data analysis was performed.

For the development of the analysis, a form was prepared with the following items: title, authors, year, database, country of origin and level of evidence.

> For the categorization of the level of evidence, seven levels of classification were considered: level 1, systematic review, or meta-analysis of controlled clinical trials; level 2, well-designed randomized controlled clinical trial; level 3, controlled clinical trial without randomization; level 4, well-designed cohort or case-control studies; level 5, systematic review of qualitative and descriptive studies; level 6, descriptive or qualitative studies and level 7, opinion of authorities and experts (GALVÃO, 2006).[4]

[3] As revisões integrativas têm o potencial de evidenciar compreensão abrangente sobre assuntos específicos e apontar lacunas existentes no conhecimento. As etapas seguidas na elaboração desta revisão serão: estabelecimento da questão da pesquisa, busca na literatura, avaliação dos dados, análise dos estudos incluídos, interpretação dos resultados e apresentação da revisão (SOUZA; SILVA; CARVALHO, 2010).

[4] Para a categorização do nível de evidência, foram considerados sete níveis de classificação: nível 1, revisão sistemática, ou metanálise de ensaios clínicos controlados; nível 2, ensaio clínico controlado randomizado bem delineado; nível 3, ensaio clínico controlado sem randomização; nível 4, estudos de coorte ou caso-controle bem delineados; nível 5, revisão sistemática de estudos qualitativos e descritivos; nível 6, estudos descritivos ou qualitativos e nível 7, opinião de autoridades e especialistas (GALVÃO, 2006).

The paper was a review, so there was no need for an opinion from the Ethics Committee.

Results

Between fifty-four articles selected in the full data search, between May and June 2020, only five publications were included in the study in the Medical Literature Analysis and Retrieval System Online (MEDLINE) database, in the search engine of the National Library of United States Medicine (PubMed), they are shown in Table 1.

Table 1 - Number of publications found in the databases and included in the study

Database	Search engine	Found	Included
MEDLINE	PubMed	54	5

Source: Devised by the author.

Table 2 shows the characterization of the articles, also considering the level of evidence. The five articles included in the review were published in English in the year 2020. Most of the research was carried out in the United States (n = 3).

Table 2 - Characterization of publications and levels of evidence of articles included in the review

N°	Title	Authors	Year	Journal	Country	Level of evidence
1	Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic.	Belhadjer, Z.; Méot, M.; Bajolle, F.; Khraiche, D.; Legendre, A.; Abakka, S.; Auriau, J.; Grimaud, M.; Oualha, M.; Maurice, B.; Wacker, J.; Ovaert, C.; Hascoet, S.; Selegny, M.; Malekzadeh-Milani, S.; Maltret, A.; Bosser, G.; Giroux, N.; Bonnemains, L.; Bordet, J.;	2020	CIRCULATION	France	6

		Filippo, S.; Mauran, P.; Falcon-Eicher, S.; Thambo, J.; Lefort, B.; Moceri, P.; Houyel, L.; Renolleau, S.; Bonne, D.				
2	Pediatric Crohn's disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab	Dolinger, M.; T; Person, H.; Smith, R.; Jarchin, L.; Pittman, N.; Dubinsky, M. C.; Lai, J.	2020	Journal Pediatric Gastroenterology and Nutrition	United States	6
3	COVID-19–Associated Pediatric Multisystem Inflammatory Syndrome	Leon, M. P. D.; Redzepi, A.; McGrath, E.; Abdel-Haq, N.; Shawaqfeh, A.; Sethuraman, U.; Tilford, B.; Chopra, T.; Arora, H.; Ang, J.; Asmar, B.	2020	Journal of the Pediatric Infectious Diseases Society	United States	6
4	Pediatric Coronavirus Disease-2019–Associated Multisystem Inflammatory Syndrome	Shulman, T, S.	2020	Journal of the Pediatric Infectious Diseases Society	United States	6
5	Multisystem Inflammatory Syndrome with Features of Atypical Kawasaki Disease during COVID-19 Pandemic	Rauf, A.; Vijayan, A.; John, S. T.; Krishnan, R.; Latheef, A.	2020	The Indian Journal of Pediatrics	India	6

Source: Devised by the author.

The data analysis is shown in figure 3, which points out the results of the studies that allowed the classification in only one category: "Scientific production on the correlation of Pediatric Inflammatory Syndrome with SARS-CoV-2".

Scientific production on the correlation of Pediatric Inflammatory Syndrome with SARS-CoV-2

Among the articles that point to the association of SARS-CoV-2 with Pediatric Inflammatory Syndrome, five articles published, mostly, in medical journals were classified in this category. Table 3, briefly describes each of the studies, covering design, population sample and main results.

Table 3 - Design, population sample and main results of the studies

N°	**Design**	**Objective**	**Population sample**	**Main results**
1	Descriptive	Describe a new complex syndrome in 35 children hospitalized for acute heart disease	Children N= 35.	Thirty-five patients met the inclusion criteria: febrile cardiogenic shock or left ventricular dysfunction and inflammatory state. SARS-Cov-2 infection was confirmed in 31/35 patients (88.5%). Nasopharyngeal swab polymerase chain reaction (PCR) was positive in 12 patients (34%) and fecal PCR in 2 patients (6%). Thirty (86%) patients had positive antibody tests: 23 had IgA and IgG, 3 had IgG, 2 had IgG and IgM and 2 had only IgA. In addition, two patients were negative for SARS-CoV-2 PCR, but had characteristics typical of lung tomography of COVID pneumonia. All patients had a severe inflammatory state, evidenced by elevated C-reactive.
2	Descriptive	Describe a case of severe COVID-19 infection in a pediatric patient recently diagnosed with Crohn's disease.	Child N= 1.	The authors declare that it is the first case of Crohn's disease recently diagnosed with suspected multisystemic inflammatory syndrome in children (MIS-C) time related to COVID-19. According to the authors, the cytokine storm was considered a main cause of morbidity in patients with severe infection by COVID-19.
3	Descriptive	Describe a case of a possible link between coronavirus disease 2019 (COVID-19) and	Child N= 1.	COVID-19 infection in children was typically milder than in adults. Pediatric presentations of COVID-19 were diverse; however, uncommonly serious cases have been reported.

		a Kawasaki-like illness and shock in Europe.		The absence of presentations similar to our case in recent publications in China may indicate a genetic predisposition for cardiac complications or an inflammatory condition previously not recognized as a response to COVID-19. We urge increased surveillance of cardiovascular disease complications, including Kawasaki disease-like disease (KD), myocarditis and febrile shock in children with COVID-19.
4	Descriptive	Describe and characterize proposed cases of coronavirus-2019 disease (COVID-19) associated with multisystemic inflammatory syndrome in children (MSI-C).	Children ≅100 in New York, 8 in London, 10 in Italy, 6 in Philadelphia.	Not all of them tested positive for polymerase chain reaction (PCR) and/or immunoglobulin (Ig) G and/or IgM antibody to severe respiratory coronavirus syndrome 2 (SARS-CoV-2). Laboratory studies included markers of inflammation, particularly high D-dimers, ferritin and triglycerides (highly suggestive of activation syndrome macrophages [MAS]), as well as very high and extremely high cardiac enzymes and troponin N-terminal-pro Type B natriuetic peptide (NT-pro-BNP). Timely, these diseases started to manifest approximately 1 month or more after the peak of COVID-19 cases in their region, instead of contemporaneously with the peak in these heavily impacted areas. Interestingly, children with this syndrome were not described in the first series of pediatric cases in hyper-epidemic SARS-2 locations in China and Italy. Surprisingly, there is no evidence that multisystemic inflammatory syndrome (MIS-C) has occurred in children in Asia.The clinical features of MIS-C include much more impressive abdominal pain, diarrhea, vomiting and involvement of various organs, including acute kidney injury, and relatively few classic KD criteria when compared to children with KD. Cardiac characteristics of MIS-C most dramatically show moderate to very severe myocardial involvement (manifested by imaging and

				surprisingly high NT-pro-BNP troponin levels), much higher than that associated with KD or KD shock syndrome.
5	Descriptive	Describe inflammatory syndrome with clinical characteristics simulating Kawasaki disease during the COVID-19 pandemic	Child N= 1.	The laboratory features were neutrophilia, elevated PCR and clinical features including abdominal pain, gastrointestinal symptoms, myocarditis and shock. Diagnosis of "atypical" KD performed on patients who have atypical or unusual clinical features. Although some evidence of myocarditis has been observed in more than 50% of patients in the acute phase of KD, symptomatic myocarditis with cardiogenic shock is rare. The infection by COVID and KD is not conclusively proven. However, as similar reports came from several countries with a temporal relationship to COVID infection in the community, pediatricians in general need to be aware of such atypical presentations and perform early referral to tertiary care.

Source: Devised by the author

Pediatric Inflammatory Multisystem Syndrome (PIMS) is described by the authors as a similar syndrome with Kawasaki Disease (KD), with the exception of only one study, which characterizes the syndrome as the main diagnosis (RAUF *et al.,* 2020).

One study contradicts the diagnosis of Kawasaki Disease (KD) due to the clinical features of MIS-C which include much more impressive abdominal pain, diarrhea, vomiting and involvement of various organs, including acute kidney injury, high levels of troponin (NT-pro-BNP), much higher than those associated with KD or KD shock syndrome, which characterizes few classic KD criteria (SHULMAN, 2020).

All of these were descriptive case studies and show that the pathology associated with COVID-19 (recent or previous history), generates febrile cardiogenic shock or left ventricular dysfunction, myocarditis, elevated PCR and severe inflammatory state with the production of inflammatory markers.

According to one of the authors, the disease had temporarily started to manifest approximately 1 month or more after the peak of COVID-19 cases, however, the information available in the literature on this theory is insufficient (SHULMAN, 2020).

The genetic predisposition for cardiac complications or an inflammatory previously unrecognized response to COVID-19 must be taken into account, it is of paramount importance to increase surveillance (LEON, 2020), even with a low epidemiological profile, its severity is unquestionable (SHULMAN, 2020).

Discussion

SARS-CoV-2 infection in children is thought to be relatively mild compared to adult patients and often asymptomatic or minimally symptomatic. To date, knowledge of possible cardiovascular injury related to SARS-CoV-2 in pediatric patients population is limited. However, recently there has been an unexpectedly large number of children admitted to intensive care units for cardiogenic shock or acute left ventricular dysfunction in the setting of a multisystemic inflammatory state, with a large proportion of those who tested positive for SARS-CoV -2 (BELHADJER *et al.,* 2020).

> Case reports and small series described a presentation of acute illness accompanied by a hyperinflammatory syndrome, leading to multiple organ failure and shock. The initial hypotheses are that this syndrome may be related to COVID-19 based on initial laboratory tests that show positive serology in most patients (WHO, 2020).[5]

This rare syndrome that affects children shares common features with other pediatric inflammatory conditions, including: Kawasaki disease, toxic staphylococcal and streptococcal shock syndromes, bacterial sepsis and macrophage activation syndromes. It may also show unusual abdominal symptoms with excessive inflammatory markers (DAIC, 2020).

Numerous questions are raised by the recognition of the very new MIS-C. These are related to its definition, pathogenesis, epidemiology, genetics, susceptibility, diagnosis, therapy and sequelae and others. The journey is just beginning (SHULMAN, 2020).

Therefore, there is an urgent need to collect standardized data describing clinical presentations, severity, results and epidemiology (WHO, 2020).

[5] Relatos de casos e pequenas séries descreveram uma apresentação de doença aguda acompanhada de uma síndrome hiperinflamatória, levando a falência e choque de múltiplos órgãos. As hipóteses iniciais são de que essa síndrome pode estar relacionada ao COVID-19 com base em testes laboratoriais iniciais que mostram sorologia positiva em maioria dos pacientes (WHO, 2020).

Conclusion

The study showed that the analysis of scientific production on Pediatric Inflammatory Multisystem Syndrome demonstrates the possibility that the syndrome is related to SARS-CoV-2, which differentiates it from Kawasaki Disease by numerous determinants.

There is some disagreement about the time of immunological window for the development of the syndrome, however, it is accepted that children (with recent infection or who had a previous history of the Diagnosis of COVID-19) had the development of the pathology.

REFERÊNCIAS

BELHADJER, Z. *et al*. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. **Circulation**, Paris, 2020. Available: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.048360. Access: May 2020.

BOSTON CHILDREN'S HOSPITAL. **COVID-19 and a serious inflammatory syndrome in children**: unpacking recent warnings. Boston,2020.

DAIC. Delivering news, technologies, trends on cath labs across the country. **Kawasaki-like inflammatory disease affects children with COVID-19**. [S. l.], 2020.

DOLINGER, M. T. *et al*. Pediatric Crohn's disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. **Journal Pediatric Gastroenterology and Nutrition**, New York, 2020. Available at: https://journals.lww.com/jpgn/Abstract/9000/Pediatric_Crohn_s_Disease_and_Multisystem.96044.aspx. Acess: May 2020.

LEON, M. P. D *et al*. COVID-19-Associated pediatric multisystem inflammatory syndrome. **Journal of the Pediatric Infectious Diseases Society**, Michigan, 2020.

LOS ANGELES CHIELDREN'S HOSPITAL. **Multisystem inflammatory syndrome in children (MIS-C)**: what parents should know. Los Angeles, 2020.

RAULF, A. *et al*. Multisystem inflammatory syndrome with features of atypical kawasaki disease during COVID-19 pandemic. **The Indian Journal of Pediatrics**, Kerala, 2020.

SHULMAN, S. T. *et al*. Pediatric coronavirus disease-2019-associated multisystem inflammatory syndrome. **Journal of the Pediatric Infectious Diseases Society**, Chicago, 2020.

SOCIEDADE BRASILEIRA DE PEDIATRIA EM SÃO PAULO. **Síndrome inflmatóra multissistêmica pediátrica (síndrome associada temporalmente ao COVID-19)**. São Paulo, 2020.

SOUZA, M. T.; SILVA, M. D.; CARVALHO, R. Revisão integrativa: o que é e como fazer. **Einstein**, São Paulo, v. 8, n. 1, p. 102-106, 2010.

WHO. Word Health Organization. **Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19**. [S. l.], 2020.

How to quote this article

UCHIYA, Eduardo Haruo. Multisistemic Pediatric Inflammatory Syndrome (PIMS) and the association with SARS-COV-2. **Temas em Educ. e Saúde**, Araraquara, v. 16, n. 1, p. 9-20, jan./jun., 2020. e-ISSN 2526-3471. DOI: https://doi.org/10.26673/tes.v16i1.13759

Submitted: 05/04/2020
Required revisions: 05/06/2020
Approved: 10/06/2020
Published: 19/06/2020