Artículo de Revisión

Symptomatology, diagnosis, and treatment of multisystemic inflammatory syndrome in post Covid-19 infants: literature review

Sintomatología, diagnóstico y tratamiento del síndrome inflamatorio multisistémico en infantes post Covid-19: revisión bibliográfica

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Abstract: In 2020, COVID-19-associated multisystem inflammatory syndrome in children was first reported, which can have a severe course and may require supportive care. To review the scientific literature on symptomatology, diagnosis, and treatment of multisystemic inflammatory syndrome in children with COVID-19. A systematic review of publications indexed in the following browsers was performed: Pubmed, Scopus, Web of Science, since 2017, those that had some relation with the subject to be treated were chosen, in a complementary way this search was performed using the keywords. A total of 26 articles related to the topic were found, reflecting that multisystemic inflammatory syndrome is present in a large percentage of children who suffered COVID-19, MIS is characterized by fever, gastrointestinal manifestations, changes in the oral mucosa and skin rash. Laboratory and imaging tests are used to diagnose this pathology. Treatment consists of applying mainly IV immunoglobulin. Being a pathology of recent appearance in children it is important to study it and define the different components for an adequate diagnosis and treatment.

Keywords: multisystemic inflammatory syndrome, covid-19, symptomatology, diagnosis, children.

Resumen: En el 2020 se informó por primera vez sobre el síndrome inflamatorio multisistémico asociado a COVID-19 en niños, el cual puede tener un curso severo y puede requerir apoyo de cuidados. Examinar en la literatura científica sobre sintomatología, diagnóstico y tratamiento del síndrome inflamatorio multisistémico en niños con COVID-19. Se realizo una revisión sistemática de publicaciones indexadas en los siguientes exploradores: Pubmed, Scopus, Web of Science, desde el año 2017, se escogieron aquellos que tuvieron alguna relación con la temática a tratar, de forma complementaria esta búsqueda se realizara utilizando las palabras claves Se encontró un total de 26 artículos relacionados con el tema que reflejan que el síndrome inflamatorio multisistémico se encuentra presente en un gran porcentaje de niños que sufrieron COVID-19, el MIS se caracteriza por presentar fiebre, manifestaciones gastrointestinales, cambios en la mucosa oral y erupción cutánea. Para el diagnostico de esta patología se emplean exámenes de laboratorio e

imagen. El tratamiento consiste en aplicar principalmente inmunoglobulina IV. Al ser una patología de reciente aparición en niños es importante estudiarla y definir los diferentes componentes para un diagnóstico y tratamiento adecuado.

Palabras clave: síndrome inflamatorio multisistémico, covid-19, sintomatología, diagnostico, niños.

Introduction

In 2019, the first cases of a new disease occurred in China, which produced flu-like symptoms such as hyperthermia, headache, cough and dyspnea (1), which was determined to be caused by a coronavirus called SARS-CoV-2, which is highly transmissible by respiratory route (2,3). This type of virus can affect both adults and children; in children it produces multisystemic inflammatory syndrome (MIS-C).

This syndrome usually presents between 2 and 4 weeks after the presentation of COVID-19 and is diagnosed by imaging and laboratory tests. Despite being a syndrome with a low mortality rate of 2% (4), it is important that upon suspicion of this pathology, early diagnosis is made and timely management is provided, since its clinical presentation can cause serious problems in the heart, lungs or kidneys (5).

On the other hand, MIS-C, being a pathology of recent appearance due to the current pandemic, has been confused with Kawasaki disease, because some symptoms are similar in both conditions, including hyperthermia, edema of the hands or feet, rash, conjunctivitis. But unlike Kawasaki disease, MIS-C presents with stomach pain, vomiting or diarrhea. Therefore, a review on this subject is important to raise awareness of the symptomatology, diagnosis and treatment of MIS-C (6).

The bibliographic review arose from the need to broaden the knowledge on multisystemic inflammatory syndrome, as well as to determine its symptomatology, diagnosis, treatment in this age group and the need to establish a clear difference between multisystemic inflammatory syndrome and Kawasaki disease. This research will bring multiple educational benefits that will contribute to the training of health care professionals at all levels of care, who will have an updated document on this pathology. It has been verified that COVID-19 is associated with different pathologies, in children it is associated with multisystemic inflammatory syndrome (MIS-C) which is characterized by hyperthermia, altered values of inflammation markers and dysfunction of one or multiple organs, exanthema, edema of upper and lower limbs (7). These symptoms resemble those of Kawasaki disease but differ in that MIS-C presents with lightheadedness, abdominal pain, markers of inflammation and positive cardiac enzymes (8).

Within this context, the common signs and symptoms of multisystemic inflammatory syndrome (MIS-C) depend on the parts of the body that have been affected, but usually include rash, conjunctivitis, edema of the extremities, mucous membrane changes, vomiting, edema of the hands or feet, headache, lightheadedness, abdominal pain, diarrhea, hyperthermia lasting 24 hours or more, markers of inflammation, and positive cardiac enzymes (8). Finally, multisystemic inflammatory syndrome is a condition in which various parts of the body may become inflamed, including the lungs, kidneys, brain and heart, skin, eyes or gastrointestinal organs. According to recent studies, this pathology affects only children up to 8 years of age, provided they have had a positive diagnosis for COVID-19 (7). This syndrome usually appears from the second week to the sixth week post-

diagnosis of COVID-19 (8), most of the children who develop it evolve favorably with medical treatment, while other children suffer a serious affection to their organs, for which they need advanced interventions and in severe cases they are admitted to the ICU for an integral treatment, in which a multidisciplinary team intervenes (4).

The general objective of this bibliographic review is to examine the scientific literature on symptomatology, diagnosis, and treatment of multisystemic inflammatory syndrome in infants with covid-19. On the other hand, the specific objectives are to describe the symptoms in children with covid-19 diagnosed with multisystemic inflammatory syndrome according to the systematic review and to review the scientific evidence on diagnosis and treatment in children with Covid-19 presenting with multisystemic inflammatory syndrome.

Methodology

The research was systematic by means of a literature review. To carry out this process, the recommendations of the PRISMA method were followed (9).

Search strategy

The research was through the following databases: Medline, Scopus, Proquest and Web of Science, in the period between the end of 2017 and 2021. Those that were related to COVID-19 and Multisystemic inflammatory syndrome were selected, the keywords related to the desired objectives, according to the Mesh and Decs terms: "Multisystemic inflammatory syndrome", "COVID-19", "SARS-CoV2", "Symptomatology", "children", and the connections of these were made with Boolean connectors "AND" and "OR". After a first search, each article was reviewed according to title and abstract; those that had a description of the clinical variables and that presented Kawasaki disease and COVID-19 were included. However, in cases in which the study methodology was not clear and the results were not precise, the article was excluded.

Inclusion criterio

The selection of articles was made as follows:

- Languages: studies were included in Spanish and English, since the subject of COVID -19 has been widely studied, for which translators specialized in the medical area were used.
- Year of publication: between the end of 2017 and the beginning of 2021.
- Children's items with COVID-19 and Kawasaki.
- Quality of the articles.
- Studies published in high impact journals

Exclusion criteria

- Articles that were not of the year of publication sought were excluded from the study.
- Letters to the editor.
- Unable to retrieve the full text of the article.
- Repeated item from a previous search.
- Studies published in low impact journals

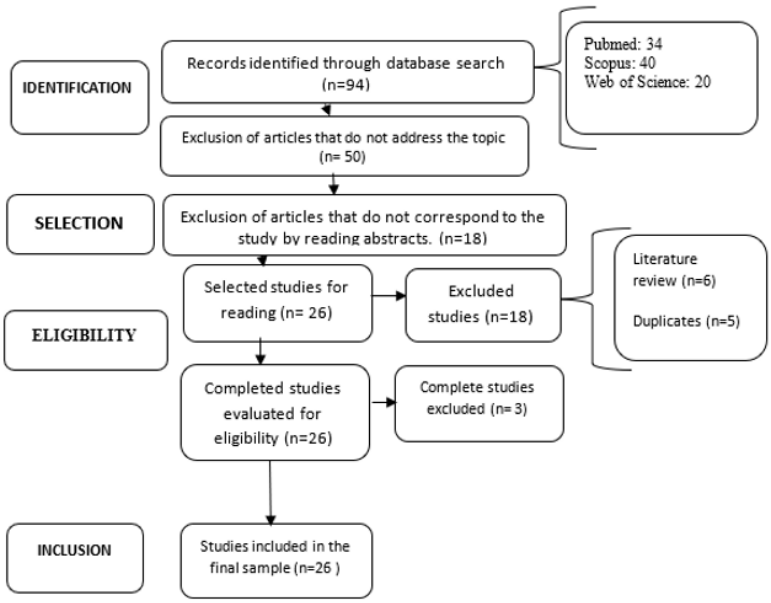
Evaluation of the quality of the study

The guidelines of the Consolidated Standards for Reporting Trials (CONSORT-2010) were used to assess the quality of the studies (10). This checklist was used worldwide to improve reported randomized controlled clinical trials using a list of 25 items to assess the title (including the type

of design), preparation of the abstract (structured and complete), background and explanation of rationale, definition of objectives and hypotheses, description of the trial design (including major changes in methods after trial initiation and reasons), the eligibility criteria for participants, the setting and location where data were collected, description of the intervention (with sufficient detail to allow for replication), fully defined outcome measures, sample size calculation (or power analysis), the method used to generate the sample data. The method used to generate the randomization sequence (including type of randomization), use of blinding methods, statistical procedures used for analyses, description of results (including comparison at baseline), discussion of results (including limitations and generalization), and other information (registry, protocol, and funding).

Processing

The data obtained were summarized in tables, in which the main characteristics of multisystemic inflammatory syndrome and its relationship with COVID-19 in children were presented. The following steps were followed, in the first stage, the subject and the formulation of the research question were identified through the PICO strategy (Population, intervention, control and outcome), having as questions, what is multisystemic inflammatory syndrome? What are the symptoms of multisystemic inflammatory syndrome? What are the methods of diagnosis of multisystemic inflammatory syndrome? and What is the treatment of multisystemic inflammatory syndrome?



Graphic 1. Search flow-chart

In the second stage, the inclusion criteria were applied as original articles related to the Multisystemic Inflammatory Syndrome and COVID-19 in children, published in Spanish and English; with full text and online. The exclusion criteria were those published up to five years previously, studies with unexplained methodologies, letters to the editor, impossibility to retrieve the full text of the article, repeated articles from a previous search and studies published in low impact journals.

In the third stage, the selection was carried out as previously explained at the time of the review of the articles; if the article was chosen after reading the abstract, it was reviewed in depth.

Then, in the fourth and fifth stages, the evaluation of the studies and the interpretation of the results obtained was carried out with more criteria, to reach the sixth stage where the discussion and synthesis of knowledge took shape; the summary of the data was placed in a matrix prepared by the author,

and finally the data obtained were compared with those of other research studies to structure the final review article.

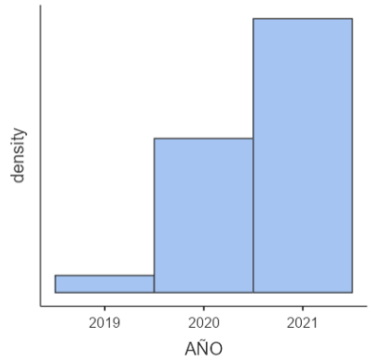
Results

Table 1. Selected articles

Authors	Year	Diagnostic	Treatment
Rodríguez, et al. (1)	2020	Hemogram	Immunoglobulin Methylprednisolone Acetylsalicylic acid (ASA) Inotropics
Taffarel, et al.(4)	2021	Chest X-rays. Laboratory tests (elevated levels of white blood cells, platelets, C-reactive protein)	Corticosteroids
Álvarez, et al. (5)	2020	Hemogram Echocardiography	Corticosteroids Anakinra Intravenous immunoglobulin (IVIG) Acetylsalicylic acid
Raab. (6)	2019	Echocardiogram	Aspirin Immunoglobulin IV
Fallas, et al. (7)	2021	Blood count, biochemistry, coagulation Cardiac markers Echocardiography Chest X-ray, TAC scan Abdominal ultrasound Electrocardiogram Electrocardiogram	Intravenous immunoglobulin Corticosteroids Heparin Aspirin
Hernández, et al. (8)	2021	Hemogram	----------
Pérez E. , et al.(11)	2021	Leukocytosis, platelets, C-reactive protein, procalcitonin, Dimer, ferritin, IgM, IgG, blood culture and echocardiography.	Admission to the intensive care unit with multidisciplinary care, immunoglobulin 2g/kg, aspirin 50 mg/kg/day, enoxaparin in prophylactic dose.
Yagnam, et al. (12)	2021	Echocardiography, creatine, kinase and its MB, fraction Troponin T, Pro- brain, natriuretic pro- peptide (proBNP), Electrocardiogram	Immunoglobulin, methylprednisolone
Sánchez, et al. (13)	2021	Echocardiogram Electrocardiogram	Intravenous immunoglobulins
De Coll, et al. (14)	2020	Echocardiogram, chest X-ray, electrocardiogram, hemogram	Intravenous immunoglobulin (IVIG) at 2 gr/kg/dose Acetylsalicylic acid (ASA) (initially at 50-80 mg/kg/day and then at 5 mg/kg/day after 48 hours afebrile) Corticosteroids (prednisone or methylprednisone) at 2 mg/kg/day for 5 days (then progressive tapering completing 2 weeks).
Ensinck, et al. (15)	2021	Evidence of coagulopathy, elevated values of markers of inflammation Increased CRP, ESR, fibrinogen, procalcitonin, D- dimer, ferritin, lactate dehydrogenase or interleukin 6 (IL-6). Decrease in serum albumin. TAC Thoracic ultrasound Abdominal ultrasound ECG Echocardiogram	Intravenous Immunoglobulin Acetylsalicylic acid
Álvarez, et al. (16)	2021	Alterations in the values of inflammatory markers, particularly C-reactive protein (CRP), ferritin and interleukin-6 (IL-6).	Management of vital signs Hydration Electrolytes and patient's metabolic status Intravenous immunoglobulin Steroids such as dexamethasone Aspirin and low- molecular-weight heparin
Morilla, et al. (17)	2021	Hemogram Chest X- ray	----------

Authors	Year	Diagnostic	Treatment
Götzinger, et al. (18)	2020	Chest X-ray, laboratory tests	Corticosteroids Intravenous immunoglobulin Tocilizumab Anakinra Siltuximab
García, et al. (19)	2021	Inflammatory markers. HemogramCoagulation. Blood chemistry. Cardiac markers. Chest X-ray. Simple chest X-ray Lung ultrasound Abdominal ultrasound or TAC scan. Echocardiography	Intravenous immunoglobulin (IVIG): should be administered at a dose of 2 g/kg Corticosteroids: *Mild-moderate disease: intravenous methylprednisolone at 1-2 mg/kg/day for 3-5 days *Severe disease: intravenous methylprednisolone at 1-2 mg/kg/day for 3-5 days or intravenous methylprednisolone at 30 mg/ kg/day for 1-3 days (maximum of 1g).
Ulloa, et al. (20)	2020	Echocardiography. Blood count	Immunoglobulin Methylprednisolone Acetylsalicylic acid (ASA) Inotropics
Tolunay, et al. (21)	2021	Elevated C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), procalcitonin, fibrinogen, ferritin, D-dimer, lactic acid dehydrogenase or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.	Intravenous immunoglobulin in 96.2% Corticosteroids in 71.2% Anakinra in 3.8% of patients
Shioji, et al. (22)	2021	Inflammatory markers	Intravenous immunoglobulin Intravenous steroids Systemic steroids Biological therapies
Izquierdo, et al. (23)	2021	Inflammatory parameters. Hemogram. Electrocardiogram.	Immunoglobulin IV (IVIG) 2 g/kg IV to be given in 10 to 12 h Methylprednisolone2 mg/kg/day IV (without hemodynamic compromise and not severe inflammation) 10 mg/kg/day IV (with hemodynamic compromise and/or severe inflammation) Acetylsalicylic acid Low molecular weight heparin
Verdugo, et al. (24)	2021	Complete blood count Coagulation tests Biomarkers	
Feldstein, et al. (25)	2021	Hemogram Laboratory tests for inflammation Chest X-ray Echocardiogram	Immunoglobulin Corticosteroids Anticoagulants
Whittaker, et al. (26)	2020	Chest and abdominal X-ray, echocardiography, echocardiogram	----------
Verdoni, et al. (27)	2020	Chest X-ray Echocardiography Blood count	Intravenous immunoglobulin at 2 g/kg. Aspirin at 50-80 mg/kg per day. Methylprednisolone at 2 mg/kg.
Noval, et al.(28)	2021	Hemogram	
Antúnez, et al. (29)	2021	CBC, chest x-ray, blood count, chest x- ray	----------
Nijman, et al. (30)	2020		Immunoglobulins Steroids Early consideration of biologics such as anti-TNF and anti- IL1 agents

As shown in the figure below, the articles selected for this study met the inclusion and exclusion criteria in terms of their year of publication. From the year 2019 one article was used, from the year 2020 nine articles were used and from the year2021 sixteen articles were used.



Graph 2. Year of publication of the selected articles

The following is a description of the symptoms produced by the multisystemic inflammatory syndrome in post covid-1 infants.

Table 2. Constitutional symptoms of Multisystemic Inflammatory Syndrome.

Frequency of constitutional symptoms		
Symptoms	**N**	**%**
Fever	20	76.9
Fever, myalgia	20	76.9
Fever, fatigue, general malaise	1	3.8
Fever, fatigue, malaise, myalgia, myalgia	1	3.8
Fever, fatigue, myalgia	1	3.8
Fever, lethargy	1	3.8
Fever, general malaise	1	3.8

According to this table in all the articles consulted on the subject, the authors agreed that fever is prevalent in 100% of the population studied, which can be accompanied by myalgia or other constitutional symptoms.

Table 3. Respiratory Symptoms of Multisystemic Inflammatory Syndrome

Respiratory Symptoms	**N**	**%**
Cough, dyspnea	2	14.3
Upper respiratory tract disease	1	7.1
Respiratory compromise	1	7.1
Respiratory tract infection	1	7.1
Respiratory manifestations	1	7.1
Rhinorrhea	1	7.1
Rhinorrhea, congestion, odynophagia, coughing, shortness of breath, chest pain, wheezing, lower chest wall contraction	1	7.1
Cough, shortness of breath	1	7.1
Cough, dyspnea, congestion, odynophagia, coughing, shortness of breath, chest pain, wheezing, lower chest wall contraction	1	7.1
Coughing, odynophagia, rhinorrhea, shortness of breath, bronchospasm, tachypnea	1	7.1
Cough, dyspnea, rhinorrhea	1	7.1

Cough, coryza, odynophagia, respiratory distress	1	7.1
Cough	1	7.1

This table shows that cough was the most frequent respiratory symptom in this syndrome, which may be accompanied by dyspnea or other respiratory conditions.

Table 4. Digestive Symptoms of Multisystemic Inflammatory Syndrome

Frequency of Digestive Symptoms		
Symptoms	**N**	**%**
Abdominal pain, vomiting, diarrhea	14	60.9
Abdominal pain, vomiting, diarrhea, exanthema	4	17.4
Diarrhea	2	8.7
Abdominal pain, vomiting, diarrhea, nausea, nausea	2	8.7
Diarrhea, vomiting	1	4.3

From the bibliographic review it was possible to conclude that diarrhea, vomiting and abdominal pain were the most characteristic symptoms of this pathology.

Table 5. Cardiac Symptoms of Multisystemic Inflammatory Syndrome

Cardiac Symptoms	**N**	**%**
Aneurysm	2	12.5
Cardiomegaly, Heart Failure	1	6.3
Coronary artery dilatation, aneurysm, aneurysm	1	6.3
cardiac dysfunction, pericarditis, valvulitis, coronary anomalies	1	6.3
Myocardial, pericardial, valvular or coronary dysfunction	1	6.3
Arterial hypotension or shock, findings of myocardial, pericardial, valvular dysfunction, or coronary abnormalities (including echocardiographic findings or increased troponin/ NT-proBNP	1	6.3
Hypotension or Shock, Myocardial dysfunction, pericarditis, valvulitis or coronary anomalies (including elevated ECHO or troponin/NT-proBNP findings). Evidence of coagulopathy (PT, PTT, d-dimer abnormalities).	1	6.3
Hypotension, cardiac compromise, coagulopathies.	1	6.3
Hypotension, myocardial, pericardial, valvular dysfunction, or coronary abnormalities (including echocardiographic findings or increased troponin/ NT-proBNP,	1	6.3
Myocarditis, cardiac dysfunction, electrocardiogram abnormalities	1	6.3
Pericarditis, valvulitis, tachycardia, hypotension, myocarditis, mild decrease in left ventricular ejection fraction (LVEF).	1	6.3
Tachycardia, capillary refill>2sec	1	6.3
Tachycardia, palpitations	1	6.3
Prolonged capillary refill time, hypotension	1	6.3
Shock, vasodilator cardiac arrhythmias	1	6.3

As for cardiac symptoms, aneurysms were the most frequent symptomatology in this system.

Table 6. Neurological Symptoms of Multisystemic Inflammatory Syndrome

Neurological Symptoms	N	%
Headache, meningismus, altered mental status (confusion, drowsiness), syncope	1	16.7
Headache, Confusion	1	16.7
Neurological manifestations (headache, mental status changes)	1	16.7
Headache, alteration of mental status/confusion	1	16.7
Headache, anosmia, ageusia, irritability, somnolence, drowsiness	1	16.7
Headache, irritability and epileptic seizures	1	16.7

On the other hand, in neurological symptoms headache was the most prevalent manifestation in children with MIS-C.

Table 7. Mucocutaneous changes produced by the Multisystemic Inflammatory Syndrome.

Very much skin changes	N	%
Mucosal changes	1	4.5
Conjunctivitis, signs of mucocutaneous inflammation	1	4.5
Conjunctivitis, changes in lips and oral cavity, skin rash, scaling	1	4.5
Conjunctivitis, mucocutaneous inflammation	1	4.5
Conjunctivitis, mucocutaneous inflammation	1	4.5
Erythematous rashes, conjunctivitis, inflammatory changes in the oral mucosa	1	4.5
Polymorphous skin rash, erythema, edema, conjunctivitis	1	4.5
Skin rash, oral mucosal changes	1	4.5
Skin eruption, conjunctivitis	1	4.5
Skin rash	1	4.5
Rash, conjunctival injection	1	4.5
Exanthema, conjunctivitis, inflammation of the mucous membranes	1	4.5
Exanthema, conjunctivitis, mucocutaneous inflammation	2	9.1
Exanthema, conjunctivitis, dry and reddened oral mucosa, edema, etc.	1	4.5
rash, erythema, firm induration of hands or feet or both	1	4.5
Mucocutaneous inflammation, Rash, conjunctivitis	1	4.5
Mucocutaneous manifestations	1	4.5
Rash, inflammation of soles and palms, conjunctivitis	1	4.5
Mucosal changes, edema, conjunctivitis	1	4.5
Conjunctivitis	1	4.5
Rash, inflammation of the oral mucosa, conjunctivitis, erythema, edema.	1	4.5

The Multisystemic Inflammatory Syndrome can produce mucocutaneous changes, in which cutaneous eruptions stand out, followed by exanthema and in third place conjunctivitis.

Diagnosis

According to the research carried out, it was found that timely diagnosis is of vital importance when multisystemic inflammatory syndrome is suspected in infants, since the timely approach to treatment reduces the possibility of the patient requiring admission to the ICU with multidisciplinary treatment. The different methods used for the diagnosis of this pathology will be presented below.

Table 8. Laboratory tests

Laboratory tests	N	%
Hemogram	6	40.9
Creatine kinase and its MB fraction, Troponin T Pro-brain natriuretic pro-peptide (proBNP)	1	4.5
Alterations in the values of inflammatory markers, particularly C-reactive protein (CRP), ferritin and interleukin-6 (IL-6).	1	4.5
Complete laboratory tests	1	4.5
Hemogram, inflammatory laboratory tests	1	4.5
CBC, biochemistry, coagulation, cardiac markers	1	4.5
Complete blood count, Coagulation tests, Biomarkers	1	4.5
Hemogram, inflammatory parameters	1	4.5
Leukocytosis, platelets, C-reactive protein, procalcitonin , Dimer, ferritin, IgM, IgG	1	4.5
Inflammatory markers, Hemogram, Coagulation, Blood chemistry, Cardiac markers	1	4.5
Inflammatory markers	1	4.5
Elevated C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), procalcitonin, fibrinogen, ferritin, D-dimer, lactic acid dehydrogenase or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.	1	4.5
Evidence of coagulopathy, elevated values of markers of inflammation Increased CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase or interleukin 6 (IL-6). Decrease in serum albumin.	1	4.5
Laboratory tests (elevated levels of white blood cells, platelets, C-reactive protein)	1	4.5

To diagnose multisystemic inflammatory syndrome, a series of laboratory tests were used, among which the request for a complete blood count and inflammatory markers stood out. Among these tests, if the patient presented symptoms of cardiac disease, cardiac markers were requested to rule out cardiac disease.

Table 9. Imaging Tests

Laboratory tests	N	%
Echocardiography	4	23.5
Chest X-ray	2	17.7
CT scan, thoracic ultrasound, abdominal ultrasound, ECG, echocardiogram	1	5.9
Echocardiography, chest X-ray, CT scan, abdominal ultrasound, electrocardiogram	1	5.9
Electrocardiogram	1	5.9
Chest X-ray, echocardiography, echocardiogram	1	5.9
Echocardiography, electrocardiography, electrocardiogram	1	5.9
Echocardiogram, electrocardiogram	1	5.9
Echocardiogram, chest x-ray, electrocardiogram, electrocardiogram, etc.	1	5.9
Chest X-ray, echocardiography, echocardiography	1	5.9

Chest and abdominal X-ray, echocardiography, echocardiogram	1	5.9
Chest X-ray, lung ultrasound, abdominal ultrasound or CT scan, echocardiography, echocardiography, etc.	1	5.9

In the diagnosis of multisystemic inflammatory syndrome, imaging tests played an important role. The most fundamental being the chest X-ray and echocardiography, which allowed detecting respiratory, digestive, and circulatory system affections, respectively.

Treatment

It is convenient to establish an opportune treatment before the diagnosis of Multisystemic Inflammatory Syndrome, such treatment is different for each patient since it will depend on their laboratory and imaging results. Next, the different medications used were exposed.

Table 10. Treatment

Medications	**N**	**%**
Immunoglobulin	19	100
Acetylsalicylic acid	8	42.1
Prednisone	7	36.8
Methylprednisolone	5	26.3
Biologicals (Tocilizumab Anakinra Siltuxima, Anti-TNF and anti-IL1 agents, Biological Therapy, Anakinra)	5	26.3
Heparin+ Aspirin	3	15.7
Steroids (dexamethasone)	3	15.7
Inotropics	2	10.5

According to the articles consulted in the realization of this topic, it was obtained that all the authors agreed in administering intravenous immunoglobulin 2g/kg, in addition to this, anticoagulants can be used, Aspirin 50 mg/kg/day and enoxaparin in prophylactic doses, and corticoids such as methylprednisolone at 2 mg/kg, and corticosteroids such as methylprednisolone at 2 mg/kg (11) and corticoids such as methylprednisolone at 2 mg/kg. The aforementioned treatment was considered as first line treatment.

Discussion

A systematic review was carried out in which 26 scientific articles were selected to determine the symptomatology, diagnosis, and treatment of multisystemic inflammatory syndrome in post covid -19 infants.

Symptoms of multisystem inflammatory syndrome in post Covid-19 infants

For the authors Pérez, et al. (11), Ensinck, et al.(15) and Feldstein, et al. (25), the main symptom of MIS-C is fever, which may be accompanied by myalgia or fatigue. On the other hand, respiratory symptoms such as cough, dyspnea, congestion, odynophagia, coughing, shortness of breath, chest pain, wheezing, lower chest wall contraction (29) and rhinorrhea (30).

Within this context, the most characteristic digestive symptoms of this syndrome are abdominal pain, diarrhea and vomiting (8) (26) (28), which may be accompanied by nausea and vomiting. (25). In addition to the aforementioned symptoms, the patient may present mucocutaneous symptoms,

including dry and reddened oral mucosa (7), Yagman, et al. (12) exhibit mucosal changes, edema, conjunctivitis, exanthema, and rash (14).

However, Álvarez et al. (5) state that cardiac symptoms such as pericarditis, valvulitis, tachycardia, hypotension, myocarditis, mild decrease in left ventricular ejection fraction (LVEF) , tachycardia, capillary filling>2sec (17) and hypotension (21). Similarly, Fallas, et al. also report that the neurological symptoms include headache, meningismus, altered mental status (confusion, drowsiness) and syncope. Morilla, et al. (17) state that in addition to headache, anosmia, ageusia and irritability may occur.

In view of the above, it can be concluded that multisystemic inflammatory syndrome presents a series of multisystemic symptoms, which should be addressed in a timely manner to prevent the patient from being admitted to the ICU for severe symptoms due to lack of treatment.

Diagnosis of multisystemic inflammatory syndrome in post Covid-19 infants

Multisystemic inflammatory syndrome in post-Covid-19 infants can be diagnosed by the use of both laboratory tests (18) and imaging tests. Within the laboratory examinations Taffarel, et al. (4) and Pérez, et al. (11), state that leukocytes, platelets, C-reactive protein, procalcitonin, Dimer, ferritin, IgM, IgG32, complete blood count, etc. should be requested. (20). On the other hand, Alvarez,et al. (16) The authors state that inflammatory markers, in particular C-reactive protein (CRP), ferritin and interleukin-6 (IL-6) and coagulation tests, should also be requested. (24). In addition, it is vitally important to request cardiac markers (19) to rule out any cardiac involvement.

In relation to the above, among the imaging tests for the diagnosis of MIS-C, pulmonary and abdominal ultrasound is used (19), in addition to this Sánchez, et al. (13) the combination of the two aforementioned techniques for diagnosis allows health professionals to have a holistic approach in order to establish the most appropriate treatment for the patient.

The combination of the two techniques for diagnosis allows health professionals to have a holistic approach to establish the most appropriate treatment for the patient.

Treatment of multisystemic inflammatory syndrome in infants post Covid-19

Once multisystemic inflammatory syndrome has been diagnosed, it is of vital importance that treatment be initiated to avoid health complications in the patient. For the treatment of this syndrome, Alvarez, et al (16) state that an adequate management of vital signs, hydration, metabolic status of the patient should be carried out, and in addition, medication such as intravenous immunoglobulin, steroids such as dexamethasone, aspirin and low molecular weight heparin should be used.

Despite this position, most of the authors consulted have concluded that intravenous immunoglobulin should be administered as first line treatment. This drug is applied 2 g/kg IV to be given in 10 to 12 hours. (23). On the other hand, Götzinger, et al. (18) and Shioji et al. (22) state that biologic therapy with Tocilizumab, Anakinra, Siltuximab should be considered. Izquierdo, et al. state that in addition to immunoglobulin, methylprednisolone, 2 mg/kg/day IV (without hemodynamic compromise and not severe inflammation) or 10 mg/kg/day IV (with hemodynamic compromise and/or severe inflammation) and acetylsalicylic acid (ASA) or low molecular weight heparin (LMWH) should be used (23).

As a summary of the above, the treatment of multisystemic inflammatory syndrome consists of the administration of immunoglobulin, anticoagulants, and corticoids as first line treatment, in addit ion to which steroids (dexamethasone) and biological therapy (Tocilizumab, Anakinra, Siltuximab) can be used if the case warrants it.

Conclusions

The current pandemic represented a great challenge for the health area, since there was no knowledge about Covid-19, which stimulated the investigation of this new pathology, through which it has been possible to collect initial data, evolution, and sequelae. In addition to the post-Covid-19 complications in adults, it has been determined that infants who become infected with this disease may develop multisystemic inflammatory syndrome.

This syndrome is of recent appearance, its symptomatology is varied and very similar to that of Kawasaki syndrome, but it can be differentiated only by the positive test for SARS-CoV-2. The symptoms of MIS-C mainly include fever lasting more than three days, cough, abdominal pain, diarrhea, vomiting, headache, aneurysm, polymorphous skin rash, erythema, edema, and conjunctivitis. In short, this pathology should be suspected in patients with multisystem involvement and present more than two of the above symptoms.

On the other hand, the diagnosis of this syndrome is based in the first instance on laboratory tests to look mainly for markers of inflammation and cardiac involvement; and in the second instance it is based on imaging tests to detect if there is multisystem involvement. Finally, the treatment of multisystemic inflammatory syndrome in infants post covid-19, consists mainly in the application of intravenous immunoglobulin, accompanied by anticoagulants and corticoids according to the case of each patient. In addition, in cases where severe multisystemic involvement has been detected, biologic therapy is added to the treatment.

The main limitation of this study was the minimal existence of articles with significant samples of participants, which was since the Multisystemic Inflammatory Syndrome in infants post covid-19, is of recent appearance due to the pandemic that is currently being experienced for about a year and a half. On the other hand, only complete articles available were included, which caused other relevant articles on the subject to be left aside, since for the moment they were only letters to the editor.

According to this systematic review, it is important to conduct further qualitative research to clarify the symptomatology, diagnosis, and treatment of multisystemic inflammatory syndrome in post-covid-19 infants. These studies will allow the creation of a standardized public practice guideline for the adequate approach to this pathology.

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