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Review article

SARS-CoV-2 and post-COVID-19 syndrome in paediatric rheumatology: A scoping review

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ABSTRACT

Introduction: An increasing number of musculoskeletal clinical manifestations, the onset of diseases and rheumatological manifestations have been seen in the paediatric population surviving COVID-19, however, the medical literature on the subject is limited.
Objective: To explore the available evidence on musculoskeletal symptoms and autoimmune diseases in the paediatric population with post-COVID syndrome.
Methodology: Scoping systematic review in PubMed and Scopus through search strategies. Observational and experimental studies are included in populations under 21 years of age with and without autoimmune diseases, without time limit in English and Spanish.
Results: The 28 documents included: case reports (n = 6), cross-sectional studies (n = 5), prospective cohort studies (n = 5), retrospective cohort (n = 6), case series (n = 6), ambidirectional section (n = 1), randomized controlled trial (n = 1), and longitudinal section study (n = 1). The total study population was 56,738 patients. The most frequent symptoms presented in long COVID-19 are myalgias and arthralgias. The evidence showing a relationship between SARS-CoV-2 infection in the development of musculoskeletal symptoms and autoimmune diseases in the convalescent period is limited.
Conclusions: Myalgias and arthralgias are the most frequent symptoms in long COVID. Patients with SARS-CoV-2 infection and a history of rheumatic disease who are undergoing immunomodulatory treatment do not have a dangerous risk of developing severe presentations and/or complications of the disease.

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SARS-CoV-2 y síndrome post-COVID-19 en reumatología pediátrica: una revisión exploratoria

Palabras clave:
SARS-CoV-2
COVID-19
Enfermedades reumáticas
Mialgias
Artralgias
Pediatría

RESUMEN

Introducción: En población pediátrica sobreviviente a la covid-19 se ha visto un creciente número de manifestaciones clínicas musculoesqueléticas, aparición de enfermedades y manifestaciones reumatológicas, sin embargo, la literatura médica sobre el tema es limitada.

Objetivo: Explorar la evidencia disponible sobre los síntomas musculoesqueléticos y las enfermedades autoinmunes en la población pediátrica con síndrome postcovid.

Metodología: Revisión sistemática exploratoria en PubMed y Scopus por medio de estrategias de búsqueda. Se incluyeron estudios observacionales y experimentales en población menor de 21 años con y sin enfermedades autoinmunes, sin límite de tiempo, en inglés y español.

Resultados: De los 28 documentos incluidos, se identificaron reportes de caso (n = 6), estudios transversales (n = 5), estudios de cohorte prospectiva (n = 5), cohorte retrospectiva (n = 6), series de casos (n = 3), corte ambidireccional (n = 1), ensayo controlado aleatorizado (n = 1) y estudio de corte longitudinal (n = 1). La población total objeto de estudio fue de 56.738 pacientes. Los síntomas más frecuentes en la covid-19 prolongada son las mialgias y la artralgias, en tanto que resulta limitada la evidencia que muestre una relación de la infección por SARS-CoV-2 con el desarrollo de síntomas osteomusculares y enfermedades autoinmunes en el periodo de convalecencia.

Conclusiones: Las mialgias y las artralgias son los síntomas más frecuentes en postcovid. Pacientes con infección por SARS-CoV-2 y antecedente de enfermedad reumática que se encuentren en tratamiento inmunomodulador no tienen un riesgo aumentado para desarrollar presentaciones severas o complicaciones de la enfermedad.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic represented a global public health problem due to the rapid spread of the viral infection with the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) viral infection, as well as cases of pneumonia with a high morbidity and mortality rate, mainly in older adults and pregnant women.[1,2] The development of vaccines, the application of vaccine boosters and effective medical treatments made it possible to control the rapid spread of the virus and reduce the frequency of complications associated with the acute infection. However, this has also generated an increase in long-term persistent, heterogeneous and recurrent symptoms in the population of COVID-1 survivors.[2,3]

Post-COVID syndrome (PCS) is defined as the presence of persistent or recurrent clinical manifestations that are part of COVID-19, which may even extend days, weeks or months after recovery from the disease.[4] Currently, there is increasing medical evidence describing the persistence of signs and symptoms in children who are survivors of SARS-CoV-2 infection, with or without requiring hospitalization, with fatigue and cardiovascular involvement being the main manifestations.[5] Ashkenazi-Hoffnung et al.,[6] who prospectively analyzed the persistent symptoms in 90 children who recovered from COVID-19, found that one of the most frequent reasons for medical consultation were myalgias (13.3%) and arthralgias (14.4%) between one and seven months after the onset of the infection. Even though the association with musculoskeletal involvement in patients who survive the infection is unknown, it is considered to be a chronic rheumatological consequence of COVID-19.[7]

Due to the increasing number of musculoskeletal clinical manifestations in the pediatric population of COVID-19 survivors, it is necessary to contribute to knowledge about PCS to have a favorable impact on the diagnostic and therapeutic approaches in pediatric rheumatology.[7,8] The objective of this review is to explore the available evidence on the musculoskeletal symptoms of PCS, in addition to the frequency of appearance of rheumatological diseases and manifestations that could temporally be associated with SARS-CoV-2 infection in the pediatric population.

Methodology

The present exploratory systematic review followed the steps proposed by Arksey and O'Malley,[9] which were later improved by Levac et al.[10]: 1) identify the research question, 2) search for relevant documents, 3) select the studies, 4) extract data and 5) summarize and report the results. The review answered the questions: what is the existing literature that explores the relationship between PCS and musculoskeletal clinical

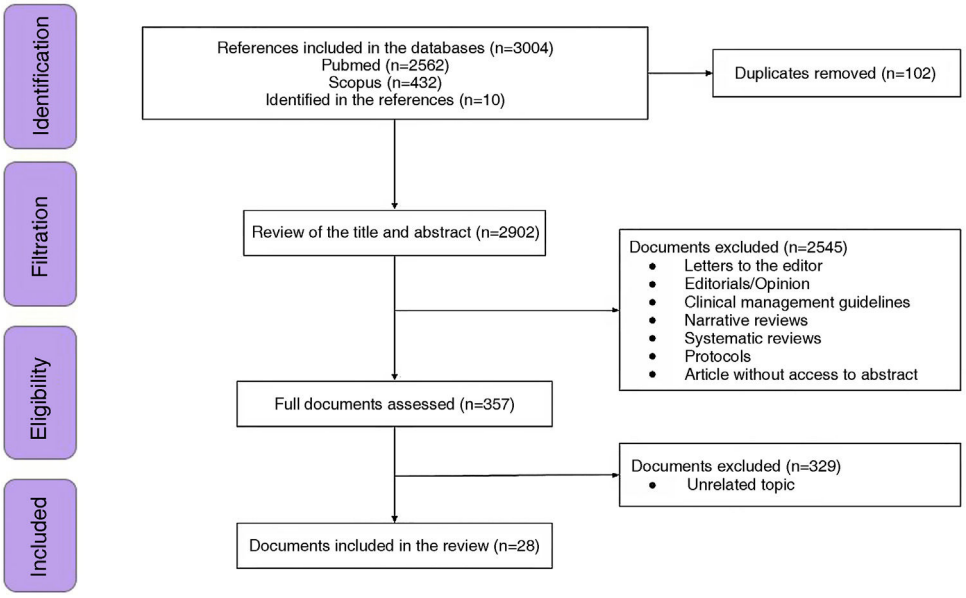

Fig. 1 – Prisma flowchart of the included publications.

manifestations in the pediatric population? and, what is the frequency of presentation of autoimmune diseases that could be associated as triggers of COVID-19?

Eligibility criteria

The inclusion criteria were: experimental and observational analytical or descriptive studies, without time limit, in English and in Spanish, that evaluate the impact of PCS on musculoskeletal manifestations in a population under 21 years of age with and without autoimmune diseases. Theoretical articles such as systematic reviews, narrative reviews, letters to the editor without case reports, position articles and documents without access to the title or abstract were excluded.

Search strategy, study selection and data extraction

The search included the PubMed and Scopus databases, using Boolean operators and keywords for each data system (Appendix Bannex 1). The authors independently reviewed and selected the titles and abstracts of the candidate publications. Finally, a debate was employed and a consensus was reached to resolve the differences between the researchers.

Duplicate manuscripts were excluded, and the selected documents were obtained in full text through the library of the Universidad de la Sabana. This step involves regular meetings to discuss and adjust the formats to the eligibility criteria. The information was then extracted from all the documents in: authors, type of document (clinical study, systematic review), characteristics of the population, objective, publication date, journal, country of the authors and main findings. The references of the articles included are found in Appendix Bannex 2.

Synthesis and presentation of the results

The presentation of the results of this review follows the categories: 1) a summary of the characteristics and the distribution of the publications included, and 2) a narrative synthesis of the results. This article follows the Prisma extension for reporting scoping reviews (Prisma-ScR)[11] (Appendix Bannex 3).

Results

Of 3004 documents identified through the searches, 102 repeated article titles, and 2545 titles and abstracts that did not meet the eligibility criteria were identified, and finally, 329 full documents were excluded because their content did not meet the objective of the manuscript (Fig. 1).

Of the 28 documents included, case reports (n = 6), cross-sectional studies (n = 5), prospective cohort studies (n = 5), retrospective cohort studies (n = 6), case series (n = 3), ambidirectional section (n = 1), controlled randomized trial (n = 1) and longitudinal study (n = 1) were identified. The total study population was 56,738 patients. The countries of origin of the authors were, most frequently, Turkey, Germany, Italy, the United Kingdom and Brazil. The general characteristics of the documents are shown in Table 1.

Case reports that correspond to a possible association between SARS-COV-2 infection and rheumatological manifestations

Sinaei et al.[12] reported the clinical case of two patients with musculoskeletal symptoms after SARS-COV-2 infection. The first case, an 8-year-old boy who presented walking limitation due to pain on the lower limb one week after having manifested respiratory symptoms and fever; the gait alteration

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Table 1 – Characteristics of the publications included.

Authors	Type of document	Characteristics of the population	Objective	Main finding/contribution	Limitations
Asadi et al.	Cross-sectional study	58 patients aged between 6 and 17 years	To describe the risk factors associated with PCS in the pediatric population	Myalgias and arthralgias were described in 5% of the population as symptoms in the PCS	Limited sample size; information bias
Borch et al.	Retrospective cohort	37,522 patients aged between 0 and 17 years	To assess the symptoms and duration of the PCS in the pediatric population with a history of PCS.	One of the most common symptoms associated with PCS was myalgia	Non-validated questionnaire; information bias
Buonsenso et al.	Cross-sectional study	128 children with a mean age of 11 ± 4 years	To assess persistent symptoms in pediatric patients previously diagnosed with PCS	Symptomatic children with a history of COVID-19 may develop myalgias and arthralgias	Limited sample size, only one interview during the study
Fink et al.	Longitudinal study	53 children aged between 8 and 18 years	To assess anthropometric, demographic and clinical data in patients diagnosed with PCS	The most frequent reason for referral of the patients was dyspnea (30 [33.3%]), followed by myalgias (12 [13.3%]) and headache (8 [8.8%])	Limited sample size, evaluation of a single pediatric center
Kikkenborg et al.	Cross-sectional study	24,637 adolescents between 15 and 18 years of age	To assess prolonged symptoms in adolescents with a history of COVID-19	Symptoms in SPC occurred with a higher frequency at 2 months and less frequently at 12 months	Monocentric
Ludvigsson	Case series and systematic review	Five patients aged between 9 and 15 years	To document persistent symptoms of COVID-19 in pediatric age	Children may experience myalgias as prolonged symptoms of COVID-19	Limited sample size
Morrow et al.	Retrospective cohort	Nine patients aged between 4 and 18 years	To describe the structure and approach of a pediatric post-COVID rehabilitation clinic	Myalgias occurred only in one patient as symptoms in PCS	Limited sample size
Osmanov et al.	Prospective cohort	518 children aged between 3 and 15 years	To assess long-term outcomes in previously hospitalized children with COVID-19 and associated risk factors	1.8% of the population had long-term musculoskeletal symptoms	Information bias
Roge et al.	Ambidirectional cohort	236 patients aged between one month and 18 years	To identify the long-term consequences of SARS-CoV-2 infection in children	Myalgias were more common in patients with COVID-19 in the acute phase versus the post-acute phase	Lack of a clear definition for PCS
Villacis et al.	Case series	55 children aged between 0 and 21 years	To analyze the clinical presentation and outcomes of COVID-19 in pediatric patients with rheumatic diseases	21.8% of the patients with a history of rheumatic diseases presented myalgias during COVID-19 and PCS	Limited sample size
Sengler et al.	Prospective cohort	76 patients aged between 11 and 16 years	To investigate the manifestations of SARS-CoV-2 infection in patients with rheumatic and musculoskeletal diseases	The patients who were symptomatic during the infection had more symptoms in the PCS than those who were asymptomatic	Limited sample size
Durcan et al.	Cross-sectional study	795 patients with a mean age of 11.05 ± 4.5 years	To assess the psychological symptoms in children and adolescents with rheumatological diseases and in their parents during the pandemic	Patients were psychologically affected since the age of 13, with higher anxiety scores in men	Absence of standardized scales

– Table 1 (*Continued*)

Authors	Type of document	Characteristics of the population	Objective	Main finding/contribution	Limitations
Smane et al.	Retrospective cohort	92 patients under 18 years of age	To describe the clinical characteristics of post-acute sequelae of SARS-CoV-2 infection	The most frequent symptoms in PCS were fatigue, myalgias and arthralgias	Limited sample size
Ashkenazi-Hoffnung et al.	Prospective cohort	Ninety patients with a mean age of 12 ± 5 years	To analyze the persistent symptoms in children after a COVID-19 infection	60% had symptoms one to seven months post-COVID-19	Limited sample size; unicentric study
Sinaei et al.	Case report	One man, 8 years; one woman, 6 years	To describe the presence of rare and severe complications in the pediatric population following COVID-19 infection	These two cases of COVID-19 in the pediatric population suggest that the virus may include a rheumatological condition	Retrospective methodology
Crivelenti et al.	Case report	One woman, 11 years	To describe the relationship between SARS-CoV-2 infection and the presence of chronic arthritis	The relationship between COVID-19 and chronic arthritis in the pediatric population cannot be ruled out	Retrospective methodology
Wintler et al.	Case report	One woman, 13 years	To describe cases of autoimmune diseases induced by COVID-19 in pediatric patients.	It seeks to support the hypothesis that COVID-19 may be an immunological trigger of autoimmune diseases in pediatric patients	
Haslak et al.	Cross-sectional study	149 patients, 90 women, with a mean age of 12.86 years	To compare the seroprevalence of SARS-CoV-2 in pediatric patients with rheumatological diseases vs. healthy patients.	Patients with rheumatological diseases who receive immunosuppressive management do not present a higher seroprevalence	Limited number of patients to estimate seroprevalence
Sözeri et al.	Retrospective cohort	4470 patients with a mean age of 12 years	To describe pediatric patients with rheumatic disease during the COVID-19 pandemic	Previous rheumatic diseases do not present an increased risk of severe SARS-CoV-2 infection	Retrospective design, without a control group
Quintana-Ortega et al.	Case report	An 11-year-old woman	To report the case of a pediatric patient with anti-MDAS JDM, with subsequent COVID-19 infection, septic shock and death	COVID-19 infection in pediatric patients with comorbidities can become a disease with severe complications	Retrospective methodology
Kearsley-Fleet et al.	Retrospective cohort	607 patients with a mean age of 14 years	To describe the clinical manifestations of patients with rheumatological diseases and severe COVID-19	Patients with jSLE, vasculitis or autoinflammatory syndromes were at higher risk of severe COVID-19 compared to those with JIA	The reported cases were confirmed and presumptive cases

– Table 1 (*Continued*)

Authors	Type of document	Characteristics of the population	Objective	Main finding/contribution	Limitations
Salvatierra et al.	Case report	A 16-year-old woman	To report the case of a patient with a diagnosis of COVID-19-related-dactylitis	Patient with edema and pain in the 2nd, 4th and 5th toes following SARS-CoV-2 infection	Retrospective methodology
Ruiz del Valle et al.	Case report	A 19-year-old man	Report the case of a 19-year-old man with a diagnosis of atypical RA due to SARS-CoV-2 infection	Patient with distal symmetrical polyarthritis associated with COVID-19	Absence of cytochemical analysis of synovial fluid
Hügle et al.	Case series	Three women and 2 men aged between 4 and 17 years	To describe patients with JIA in remission or inactive disease under treatment with a confirmed diagnosis of COVID-19	The period of time between the COVID-19 infection and the onset of joint symptoms appears to be 1 to 4 weeks	Limited number of patients
Boyarchuk et al.	Prospective cohort	51 patients aged between 2 and 18 years	To determine the frequency of COVID-19 in patients with JIA	SARS-CoV-2 infection did not present a difference in patients with JIA compared to previously healthy population	Limited number of patients with positive COVID-19
Quéré et al.	Prospective cohort	173 patients with a mean age of 11.6 years	To determine the impact of the COVID-19 pandemic on patients with JIA	The patients with JIA under treatment during the pandemic did not have an increased risk of presenting symptomatic COVID-19	The results were obtained through questionnaires for the parents
Naddei et al.	Retrospective cohort	Group A: 126 patients; group B: 124 patients	To evaluate the relapse rate of JIA in patients with a previous diagnosis during the COVID-19 pandemic	Confinement secondary to the COVID-19 pandemic is associated with an increase in the rate of JIA in the pediatric population	Retrospective methodology
Sieczkowska et al.	Randomized controlled trial	Group A: 21 patients; group B: 30 patients	To evaluate the effects of exercise at home in adolescents with JIA and jSLE during the COVID-19 pandemic	The training and the home exercise program had a positive impact on the pediatric population	Limited sample size. Limited follow-up time

JIA: juvenile idiopathic arthritis; RA: reactive arthritis; JDM: juvenile dermatomyositis; jSLE: juvenile systemic lupus erythematosus; PASC: post-acute sequelae of SARS-CoV-2 infection; PCS: post-COVID syndrome; ICU: intensive care unit.

was not related to a history of trauma. The physical examination revealed pain and limitation in movements of flexion, internal and external rotation of the left hip. The laboratory tests, which included a complete blood count and acute-phase reactants were within normal limits. The detection of IgM and IgG antigens for SARS-CoV-2 was positive and the MRI showed a joint effusion in the left hip of approximately 7 mm. A diagnosis of reactive arthritis following a viral infection was established, after which the patient received symptomatic management with non-steroidal anti-inflammatory drugs and skin traction, with total resolution of the symptoms after one week. The second case, a 6 year old girl, who consulted for fever, polyarthralgia and walking limitation predominantly in the left lower limb for one week; the patient had a history of septic arthritis in the right hip 3 years ago. The results of the X-ray of the lower limbs were within normal limits, while the ultrasound of the joints revealed the presence of mild joint effusion in both joints. As in the first case, the patient was diagnosed with reactive arthritis after the viral infection. After that, medical management was started, and as a result, a complete recovery of symptoms was observed.

Wintler et al.[13] reported the case of a 13 year-old girl with a clinical picture of 3 months of evolution consisting of edema with purpuric lesions on the extremities and back, who experienced worsening of symptoms expressed as fever, necrotic perianal lesions and exudative pharyngitis. As a response, antibiotic therapy was initiated due to a high suspicion of non-streptococcal tonsilitis. The laboratory tests on admission revealed leukocytosis, neutrophilia, anemia and positive SARS-CoV-2 immunoglobulin G and M antibodies; the immunological profile also evidenced antiproteinase 3 antineutrophil cytoplasmic (ANCA-PR3) antibody titers of 1:640 and decreased complement C4. Complementary imaging studies determined the presence of thickening of the rectal wall, moderate ascites, perianal abscess, and bilateral renal artery stenosis. The patient underwent surgical lavage and debridement due to necrotizing perianal lesion; the biopsy of perianal tissue reported leukocytoclastic vasculitis affecting small vessels with immunofluorescence staining negative for IgA. The authors diagnosed ANCA-PR3 vasculitis, for which management with methylprednisolone and rituximab was started, without ruling out a possible association between the SARS-CoV-2 infection and the development of the vasculitis.

Retrospective cohort of patients with and without rheumatic diseases

Villacis et al.[14] reported the clinical characteristics, comorbidities and medications administered in 55 patients with SARS-CoV-2 infection, of whom 81.8% (45/55) were evaluated on an outpatient basis, while 18.2% (10/55) were hospitalized. The mean age of the population was 16 years and 78.2% were women, while juvenile idiopathic arthritis (JIA) occurred in 35.6% (16/45) of the outpatient group and juvenile systemic lupus erythematosus (jSLE) in 50% (5/10) of the hospitalized patients; 21.8% of the patients with a history of rheumatic diseases presented myalgias. Active rheumatic disease (OR: 11.83; 95% CI: 1.43–558.37; p = 0.01) and severe immunosuppression (OR: 4.8; 95% CI: 3.94–1704.26; p < 0.01) were associated with a higher probability of hospitalization.

Borch et al.,[15] who worked with a cohort of 15,041 patients with diagnosed COVID-19 and a control group of 15,080 individuals, reported the main clinical manifestations and their duration. None of the patients had received the COVID-19 vaccine. An electronic questionnaire was administered to the cohort under study on two occasions, and the groups were divided according to their age group (preschoolers and schoolchildren). It was concluded that children who presented symptoms for more than 4 weeks, and those aged between 6 and 17 years reported more symptoms such as fatigue, loss of smell, muscle weakness and myalgias. The authors concluded that patients with SARS-CoV-2 infection and comorbidities presented a higher frequency of prolonged symptoms.

Sözeri et al.[16] described the clinical manifestations and the impact of the SARS-CoV-2 infection in a cohort of 84 patients with a mean age of 12 years, 35.6% of whom had a clinical history of JIA, while 34.5% experienced familial Mediterranean fever (FMF). 29.9% were under treatment with biological or conventional disease-modifying drugs. COVID-19 caused the exacerbation of the rheumatic disease in 56 children, due to discontinuation or change of the medication or to the viral infection; 18 (20.7%) of the patients met the clinical criteria for multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 (MIS-AC). It was concluded that immunomodulatory management in this population did not show an increase in the rate of complications and consequences associated with SARS-CoV-2 infection.

Prospective cohort

Sengler et al.[17] described the clinical manifestations during the evolution of the COVID-19 active infection and the convalescence period in 76 children with rheumatic diseases. The main underlying comorbidities were JIA (58%) and connective tissue disease (8%) under treatment with biologic drugs and others with systemic glucocorticoids. Of the total pediatric population evaluated, 58 patients developed mild symptoms of COVID-19. In 84% of the patients assessed, there was no evidence of increased activity of the rheumatological disease during the active infection. Finally, the authors considered that the infection did not have a major impact on the course or activity of the underlying rheumatologic or musculoskeletal disease.

Ashkenazi-Hoffnung et al.[6] reported the clinical manifestations in 90 children with persistent symptoms after COVID-19, of whom 91.1% presented mild disease, 6.7% moderate and 2.2% severe. The main persistent symptoms presented were fatigue (71.1%), dyspnea (50%) and myalgia (45.6%), which resolved at 11 and 12 weeks after the infection. Four patients who presented diseases of autoimmune origin showed no difference in the frequency of prolonged symptoms, compared to the rest of the study cohort.

Cross sectional

Haslak et al.[18] evaluated the seroprevalence of SARS-CoV-2 in 31 patients with a diagnosis of FMF, 42 with JIA, 33 with jSLE and 43 without rheumatological diseases; the study design

aimed to determine the mucosal immunity by estimating IgA seropositivity instead of IgM. The detection of antigens for IgA was positive in 10% (15/31) of the patients (8 controls, 3 jSLE, 2 FMF, 2 JIA, p = 0.196), while for IgG it was positive in 9.4% (14/31) of the patients (7 healthy controls, 5 JIA, 1 FMF, 1 jSLE, p = 0.156); 12.75% of the population presented positive antibodies for both immunoglobulins (p = 0.644). Of the IgA-positive patients, 20% were under treatment with hydroxychloroquine, 13.3% with colchicine, 6.7% with oral corticosteroids, and 6.7% with adalimumab. Rheumatic diseases and immunomodulatory management were not related to an increase in the seroprevalence of COVID-19.

Case series

Ludvigsson[19] described a series of 5 children who presented clinical manifestations consisting of fatigue, dyspnea, palpitations, headache, difficulty in concentrating and myalgias, for at least 6 to 8 months after their clinical diagnosis of COVID-19; myalgias persisted for 2 months in 3 of the 5 children assessed, while no patient required hospital management at the time of diagnosis of SARS-CoV-2 infection. The authors point out that the pediatric population may present prolonged symptoms during the convalescence period, regardless of pre-existing rheumatological diseases.

Discussion

The following scoping review synthesized the available medical evidence on the clinical impact of COVID-19 and PCS in pediatric patients with and without rheumatic diseases. The literature describes a possible relationship between SARS-CoV-2 infection and the development of musculoskeletal symptoms and autoimmune diseases in the convalescence period.[5,6,14,18,20–27] It has not been possible to determine a clear relationship between severe presentations of COVID-19, complications and PCS in pediatric patients with already established rheumatological diseases who are under treatment with biological or conventional disease-modifying drugs.[18,21,28–30] The available data on the clinical characteristics, incidence, and severity of COVID-19 and PCS in the pediatric rheumatological populations are limited, due to the small size of the sample population represented in the studies.[12,15,31–33]

The main prolonged musculoskeletal symptoms during the convalescence period were myalgias and arthralgias, which were present for at least 4 weeks.[16,19,34–36] Post-viral infection reactive arthritis is described as one of the most frequent rheumatological diseases after SARS-CoV-2 infection.[31] However, a greater number of clinical studies on the impact that rheumatological diseases may have on children with COVID-19 or PCS are necessary.[5,17,32]

It has been demonstrated that SARS-CoV-2 infection has a greater impact and rate of complications in comorbid older adults than in pediatric patients. Despite this, cases of severe complications that increase morbidity and mortality rates are reported in children, such as MIS-AC requiring mechanical ventilation, so that the tissue injury and the inflammatory status are perpetuated due to the infectious process and the specialized medical management during hospitalization.[37,38] Dennis et al.,[39] who evaluated 201 adult COVID-19 survivors, found that 42% of them had 10 or more symptoms, while 60% experienced PCS. Fatigue and myalgia were the most frequent manifestations, and the heart and lungs were the organs with the greatest deterioration 4 months after the initial symptoms of COVID-19. Even though to date the description in the pediatric population reveals a close similarity with the adults in the prolonged clinical manifestations, it is not entirely clear the impact that pre-existing rheumatological diseases, tissue damage, hyperactivation of the immune system and the chronic inflammatory state may have on these prolonged symptoms.[18,26,28,35]

In children with pre-existing rheumatic diseases under treatment with biological or conventional disease-modifying drugs and glucocorticoids, a greater predisposition to suffer a severe infection, complications or prolonged symptoms due to COVID-19 has not been described compared with the previously healthy pediatric population.[5,16–19,26–30] Diseases such as JIA and jSLE concomitant with active SARS-CoV-2 infection can manifest in a similar way to MIS-AC with fever, skin rashes, and elevated systemic inflammatory markers,[38] making it relevant to recognize a history of rheumatological diseases and immunomodulatory management in patients with serious or severe COVID-19 in whom multiple diagnoses may overlap, so that the timely therapeutic approach is delayed.

One of the rheumatic diseases that most affects the pediatric population is JIA, whose prevalence is estimated between 16 and 150 cases per 100,000 inhabitants.[40] Bacterial infections due to *Mycoplasma pneumoniae* or *Campylobacter jejuni*, and viral infections as is the case of the influenza virus, have been related to the development of JIA.[41,42] Similar data were reported with SARS-CoV-2 infection with clinical manifestations occurring within a time period of one to four weeks after the diagnosis of the viral infection.[33] In the pathophysiology, the role of the storm of proinflammatory cytokines, mainly IL-6, IL-1, IL-18, interferon gamma and tumor necrosis factor alpha, together with a state of hyperferritinemia, are associated with the musculoskeletal tissue injury and the chronic inflammatory state that predispose to the development of autoimmune diseases and musculoskeletal symptoms during the convalescence period.[43–46] In addition, the lack of medical care by the treating rheumatologist predisposes to the risk of relapse of the disease during the periods of confinement.[47,48]

In the adult population, an incidence of PCS of approximately 30% is estimated, being the main symptoms fatigue, cough, myalgia, arthralgia, insomnia and mucocutaneous alterations for up to 3 to 9 months,[49,50] in addition to the appearance of autoimmune diseases such as hemolytic anemia, immune thrombocytopenia or Guillain-Barré, among others.[49] Prolonged symptoms such as fatigue, cough, myalgia and arthralgia are reported in the pediatric population, although further evidence is needed to determine whether the musculoskeletal symptoms are a consequence of the pre-existing rheumatic diseases, the viral infection or the lack of optimal medical management.[5,16–27,29–33]

Reactive arthritis is a sterile joint inflammation caused by a distant infection in susceptible hosts, characterized by typically asymmetric monoarthritis or oligoarthritis of the lower limbs.[51,52] A considerable number of viral or bacterial

infections which could trigger autoimmune disorders in susceptible pediatric patients have been studied, including post-infectious reactive arthritis related to infections with *Yersinia* spp, *Campylobacter* spp, zika and Epstein-Barr virus[52]; however, in younger children it is necessary to make a differential diagnosis with transient synovitis, which has a strong association with viral infections.[52,53] One of the main pathophysiological mechanisms by which viral infections, including SARS-CoV-2, can trigger a reactive arthritis is due to molecular mimicry and autoreactivity in the host, which ultimately generates a chronic systemic and articular inflammatory state.[53–55].

Limitations

Two databases, PubMed/Medline and Scopus, with publications in English and in Spanish, were used in this scoping review. However, in none of the included studies was the quality of the evidence evaluated according to the Prisma-ScR guideline.[11]

One of the main limitations presented was the small sample size in many of the studies reviewed, which hinders understanding and making an adequate approach to the implications of SARS-CoV-2 infection or prolonged symptoms in the pediatric population with and without rheumatological diseases. In addition, a high percentage of articles on the clinical behavior, complications and seroconversion in patients with autoimmune diseases, without relevant data on PCS, were included. The information reported by the guardians or parents of the children could have generated biases at the time of collection of the results in the clinical studies.

Conclusions

Patients with SARS-CoV-2 infection and a history of rheumatic disease who are receiving immunomodulatory treatment do not have an increased risk of developing severe presentations or complications of the disease. The symptoms that occur most frequently in long COVID-19 are myalgia and arthralgia. Since autoimmune diseases are less frequent in the pediatric population compared with adults, the resulting information is limited, so it is necessary to have more information to complete the current data on prolonged manifestations and PCS.

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Conflict of interest

The authors declare that they have no conflict of interest that affects the preparation of this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rcreue.2024.06.001.

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