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Letter

COVID-19 in Children With Rheumatic Diseases in the Spanish National Cohort EPICO-AEP

To the Editor:

SARS-CoV-2 infection in children is relatively mild. Approximately 10% of identified cases are pediatric,[1] with a small proportion needing hospitalization. About 25–60% of children admitted with the coronavirus disease 2019 (COVID-19) have comorbidities.[2,3]

Studies in adults with rheumatic diseases (RD) show that immune-mediated inflammatory disease and use of biologics are not associated with a worse clinical outcome of COVID-19.[4,5,6,7] However, if patients have poorly controlled active RD or receive corticosteroids, they may be at an increased risk of infection and serious disease. Based on previous case series, scientific associations have released management recommendations for these patients.[8,9]

We aimed to describe the prevalence of RD among children younger than 18 years with SARS-CoV-2 infection at the 49 hospitals included in the Spanish national cohort EPICO-AEP. This study was approved by the Ethics Committee of the University Hospital 12 de Octubre (code 20/101). Informed consent was obtained from parents and mature minors.

By June 30, 2020, there were 350 children admitted to the hospital, of which 48 (13.7%) required intensive care unit admission, and 4 (1.1%) died. Among the pediatric patients admitted with COVID-19, 8 children (2.3%) had a history of RD (Table 1). The median age was 12.1 years (IQR 8.3–14.5 yrs) and all were female. COVID-19 manifested as pneumonia in 4 and as febrile syndrome and/or upper respiratory infection in 4. One of the 8 (12.5%) patients with RD died. She had severe juvenile dermatomyositis with rapidly progressive interstitial lung disease (RP-ILD) associated with anti-MDA5 that required mechanical ventilation prior to SARS-CoV-2 infection. Despite the aggressive treatment of RP-ILD, respiratory failure did not improve, and the patient developed refractory septic shock and died.

Juvenile idiopathic arthritis was the most frequent diagnosis. In 5 of 8 (62.5%) cases, the RD was not fully controlled. In 2 patients, the diagnosis of COVID-19 coincided with the onset of RD. Although 7 cases had a good clinical outcome, 2 presented with complications: deep vein thrombosis in both patients, with pulmonary bacterial superinfection in 1 patient and adrenal hemorrhage in the other (Table 1). Seven patients received corticosteroids for their underlying condition. Immunosuppressive therapy was not fully suspended for any of the patients; however, azathioprine (AZA) was withdrawn for 1 patient.

Published series agree that adult patients with RD have a similar risk of contracting a SARS-CoV-2 infection as the general population, and patients with other comorbidities like hypertension, diabetes, or cardiac diseases are at a higher risk of developing a more severe clinical course of COVID-19.[4,5,6,7] However, certain conditions, such as the presence of active disease and some immunosuppressants, increase the risk of hospitalization. The German National Register with 104 adults with RD and COVID-19 revealed that hospitalized patients were more likely to receive glucocorticoids (GCs), whereas biological disease-modifying antirheumatic drugs (DMARDs) were used less often.[4] The Global Rheumatology Alliance physician-reported registry,[5] with a total of 600 cases of COVID-19 in adults with RD from 40 countries, found that prednisone dosage ≥ 10 mg/day was associated with higher odds of hospitalization. The use of conventional DMARDs alone or in combination with biologics/Janus kinase inhibitors was not associated with hospitalization. Another Spanish series[6] with 122 adult patients with RD found that methotrexate (MTX) and rituximab therapy was a risk factor for hospital admission, but not for mortality, while other DMARDs did not show differences. However, GCs seemed to increase the risk of mortality.

Data in the pediatric population are very limited. In pediatric series, COVID-19 in children with RD were not reported.[3,10] In our series, all children received prednisone or MTX, 2 agents that have been found to increase the risk of hospitalization or serious illness in adults. A significant percentage of these adult patients were in the early stages of an uncontrolled disease.[4,5,6] Importantly, a significant percentage of our children was in the early stages of the disease, without good control. Two patients had COVID-19 at the time of onset of RD, which leads us to the hypothesis of COVID-19 possibly having a role in triggering the disease. Thrombotic complications are common in adults with COVID-19 but are rarely seen in children. In our series, 2 girls presented with such complications. One case was central venous catheter-related thrombosis, and the other was due to antiphospholipid syndrome with suspected systemic lupus erythematosus. The role that SARS-CoV-2 infection can play in this complication is uncertain in our cases.

For children with RD and COVID-19, the American College of Rheumatology (ACR)[9] recommends maintaining treatment with nonsteroidal antiinflammatory drugs, conventional DMARDs, and biological DMARDs. The ACR further recommends that GC therapy be initiated or continued at the lowest effective dose when clinically indicated. In our patients, the therapy was not modified, except for AZA withdrawal in 1 case. Most patients had active disease, and the risk of relapse was considered higher than the risk of maintaining pharmacotherapy.

In summary, children with RD from the Spanish national EPICO-AEP cohort accounted for 2.2% of hospitalized patients with COVID-19. The disease evolution has been moderately favorable, with 1 fatality. Active COVID-19 disease and the use of corticosteroids could be considered as risk factors in the pediatric population as well as in adults. More prospective studies are needed to characterize risk factors in this population.

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The authors declare no conflicts of interest.

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Table 1. Clinical characteristics of children with rheumatic diseases and SARS-CoV-2 infection.

Case No.	1	2	3	4	5	6	7	8
Age, yrs	11.7	12.6	14.8	4.3	15.2	7.2	11.5	13.7
Sex	F	F	F	F	F	F	F	F
COVID-19 close contact	Yes	No	No	No	Yes	No	Yes	Yes
Primary disease	Anti-MDA5 JDM with ILD	· cANCA vasculitis · Hemodialysis	sJIA	sJIA	Oligoarticular JIA	PFAPA	Polyarteritis nodosa	· APS · Suspicion of SLE
IS treatment/ targeted therapy	· MP pulses · Tacrolimus · MMF · CYC · Ig	· PDN 5 mg/d · AZA	MP pulses followed by PDN 1 mg/ kg/d	· PDN 1 mg/kg/d · Canakinumab	· MTX · IFX	· Intermittent PDN[a]	· PDN 2.5 mg/48 h · MTX · Colchicine · TCZ	PDN 0.5 mg/kg/d
Time since RD diagnosis	4 months	1 yr	Onset	2 months	10 yrs	2 yrs	6 yrs	Onset
Fever	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Cough	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Sore throat	Yes	Yes	Yes	No	Yes	No	No	No
Dyspnea	Yes	No	No	No	No	Yes	No	No
Lymphocytes,/mm^3 (minimum value)	0	380	1070	1080	2950	2300	2900	1200
D-dimer, ng/mL (max value; normal 0–500)	10,200	1168	829	5953	142	–	174	1194
IL-6 pg/mL (max value; normal < 4.4)	1000	–	–	–	–	–	–	–
CRP, mg/L	41.4	9	103.8	341	3	12.1	0.3	33
Ferritin, mg/dL (normal 10–291)	60,456	1270	419	5200	–	–	84	517
Chest radiograph	· Bilateral infiltrates · Severe ILD · Pneumothorax	· Normal initially · Evolution of focal infiltrate	Subtle ground-glass infiltrate in the left lung base, asymmetrical	Lobar consolidation pleural effusion	Normal	Bilateral infiltrates	Normal	Normal
Required hospitalization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
O_2 therapy	Yes	Yes	No	Yes	No	No	No	No
Treatment	· Antibiotics · HCQ · Remdesivir[b] · TCZ	· Reduction in IS (AZA withdrawal) · LPV/Rtv · HCQ[c]	· HCQ	· LPV/Rtv · Antibiotics	–	· Antibiotics	· HCQ	· HCQ · Enoxaparin
Duration of hospitalization, d	33	7	9	12	3	6	2	30
Complications	· Sepsis/shock, respiratory and renal failure · Mechanical ventilation · Death	· None	· None	· Femoral vein thrombosis (catheter-related) · Suspicion of bacterial infection	· None	· None	· None	· Femoral vein thrombosis · Adrenal hemorrhage
Seroconversion	–	Yes	–	No	No	–	Yes	–

[a] 2 mg/kg/single dose when needed; not recently. [b] Remdesivir was given for a total of 5 days at an intravenous dose of 5 mg/kg on Day 1, followed by a maintenance dose of 2.5 mg/kg. [c] According to our local guidelines at admission, the oral dose was as follows: HCQ 6.5 mg/kg/day (dosing q12h) in > 6-year-olds, and HCQ 10 mg/kg/day (dosing q12h) in children > 6 years (max daily dose 400 mg) for 5 days. Anti-MDA5 JDM: anti-melanoma differentiation-associated gene 5 juvenile dermatomyositis; APS: antiphospholipid syndrome; AZA: azathioprine; cANCA: cytoplasmic antineutrophil cytoplasmic antibodies; CRP: C-reactive protein; CYC: cyclophosphamide; COVID-19: coronavirus disease 2019 (caused by SARS-CoV-2); JDM: juvenile dermatomyositis; HCQ: hydroxychloroquine, IFX: infliximab; ILD: interstitial lung disease; IS: immunosuppressant; JIA: juvenile idiopathic arthritis; sJIA: systemic juvenile idiopathic arthritis; LPV/Rtv: lopinavir/ritonavir; MMF: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate; PDN: prednisone; PFAPA: periodic fever, aphthous stomatitis, pharyngitis, adenitis; RD: rheumatic disease; SLE: systemic lupus erythematosus; TCZ: tocilizumab.

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APPENDIX. List of study collaborators. Rheumatic Diseases EPICO-AEP Working Group. Agustín Remesal, MD, Sara Murias, MD, Fátima Ara-Montojo, MD, Enrique Otheo, MD, PhD, Francisco J. Sanz-Santaeufemia, MD, Álvaro Villarroya, MD, Clara Udaondo, MD, Cinta Moraleda, MD, PhD, Alfredo Tagarro, MD, PhD.

Correction

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