Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Editorial

About autoimmunity and COVID-19 in pediatrics

A propósito de autoinmunidad y COVID-19 en pediatría

Since the first descriptions of SARS-CoV-2 infection at the end of 2019, it has been spoken about the important autoimmune response triggered in the host after the infection with this virus, the morbidity and mortality in both the adult and pediatric populations, and the atypical and persistent manifestations that we can even observe months after the infection.

After the beginning of the SARS-CoV-2 pandemic, the first cases of hyperinflammation in pediatric patients occurred, with clinical symptoms very similar to Kawasaki disease (Kawasaki-like), Kawasaki disease shock, and hemophagocytic lymphohistiocytosis. Presentation which was called multisystem inflammatory syndrome-transiently associated with COVID (MIS-TAC). The clinical manifestations began two or three weeks after SARS-CoV-2 infection, and were given by cardiac involvement, mainly myocarditis, with or without coronary aneurysms, hyperferritinemia, hypertriglyceridemia, elevated D-dimer, altered fibrinogen, hematological and hepatic compromise, and in many cases involvement of the central nervous system, implying high morbidity and mortality in this population group.[1,2]

Nowadays it is known, although it has not been completely elucidated, that the SARS-CoV-2 virus disrupts tolerance mechanisms and triggers autoimmunity through different pathways, the most accepted being cross-reactivity, molecular mimicry, bystander activation and shared epitopes. It should not be disregarded that nearly 80% of patients with COVID-19 have a mild to moderate response, which implies that not everything is the ability of the virus to trigger an immune response, but that factors dependent on the host could be the determinants of this type of response.[3,4]

After the start of the pandemic, an increase in consultations for both organ-specific and systemic autoimmune manifestations was evident. Chilblain-like acral dermatological lesions secondary to virus-induced endothelial damage,[5] hematologic manifestations such as immune thrombocytopenic purpura (ITP) and hemolytic anemia have been described, as well as early and atypical manifestations of autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and systemic vasculitis. These reports motivated the study conducted by Dr. Restrepo in the Colombian department of Huila.

This study sought to clarify a temporal relationship between SARS-CoV-2 infection and the appearance of autoinflammatory diseases (AIDs) in patients under 15 years of age over a three-year period (September 2018–September 2021). The average monthly incidence rate was 0.81 cases/100,000 inhabitants; however, during the study period, higher incidence rates were found for ITP (1.3 cases/100,000), SLE (0.88 cases/100,000), juvenile idiopathic arthritis (0.65 cases/100,000 inhabitants) and vasculitis (0.65 cases/100,000 inhabitants), but no correlation was found between the rate of diagnoses of autoimmune diseases and the rate of cases of SARS-CoV-2 in children under 15 years of age ($p = 0.634$).[6]

Another report in Latin America, conducted by Montiel et al.[7] in Paraguay, described a series of cases of adult patients with the debut of AID on average 20 days after the onset of the symptoms of COVID-19. The most frequent complication was Guillain Barré (40%), followed by systemic vasculitis (granulomatosis with polyangiitis and leukocytoclastic vasculitis with microthrombi), cytopenias—mainly autoimmune thrombocytopenias—, one patient with thrombotic thrombocytopenic purpura (TTP), and SLE. Lim et al.[8] published in 2023 an increased risk of AID and connective tissue disorders following SARS-CoV-2 infection, being the main related diseases alopecia areata (aHR 1.12), ANCA-related vasculitis (aHR 2.76), Crohn's disease (aHR 1.68) and sarcoidosis (aHR 1.59). Although these studies tell us about the growing number of patients who present post-COVID-19 AID, their objective was not to determine the severity of these manifestations, a reality

DOI of original article: https://doi.org/10.1016/j.rcreue.2024.09.001.

that we see reflected in our post-pandemic patients, who are presenting with severe and atypical manifestations of classic rheumatic diseases, but we do not have studies that describe this phenomenon in detail.

Another manifestation of autoimmunity is the presence of antinuclear antibodies (ANA) in 44% of patients who suffered from COVID-19, in titers >1/160 one year after the infection, related to the presence of signs of neurocognitive compromise, unlike the patients who were ANA negative.[9] Likewise, it has been described the presence of titers of antiphospholipid antibodies and antineutrophil cytoplasmic antibodies (ANCA) after the infection. On the other hand, the terms "Long-COVID" or severe post-acute sequelae of SARS-CoV-2 infection (PASC) have emerged to refer to the persistence of symptoms such as dyspnea, musculoskeletal pain, depression or sleep disorders, which may persist three months after the infection, although in the pediatric population cases have been reported up to 8 weeks later.[10] Diabetes mellitus and severe acute hepatitis of unknown etiology were also associated with SARS-CoV-2 infection.[11,12]

With this interesting Colombian study, which reminds us and highlights the growing body of evidence on the association COVID-19 and AID, we cannot forget this virus that is here to stay and that has come to significantly change the way we see autoimmunity and rheumatic diseases that appear in childhood; the health systems must adopt measures to establish an adequate and timely diagnosis and establish a proper treatment in the light of the current circumstances.

REFERENCES

1. Freire-de-Lima L, Scovino AM, Delgrosso S, Silva M, Santos E, Ramos M, et al. Autoimmune disorders & COVID-19. Medicines (Basel). 2021;8:55, http://dx.doi.org/10.3390/medicines8100055.
2. Ramos-Casals M, Brito-Zerón P, Mariette X, Aube B, Lopes M, de Ramon C, et al. Systemic and organ-specific immune-related manifestations of COVID-19. Nat Rev Rheumatol. 2021;17:315–32, http://dx.doi.org/10.1038/s41584-021-00608-z.
3. Shah S, Danda D, Bhatia A, Jain S, Babu G, Dhillon S, et al. Autoimmune and rheumatic musculoskeletal diseases as a consequence of SARS-CoV-2 infection and its treatment. Rheumatol Int. 2020;40:1539–54, http://dx.doi.org/10.1007/s00296-020-04639-9.
4. Icenogle T, Miller K, Barnett J, Morrow K, Gupta R, Stankus J. Infection or autoimmunity. Front Immunol. 2020;11:2055, http://dx.doi.org/10.3389/fimmu.2020.02055.
5. Colmenero I, Santonja C, Moreno A, Gallego M, Cifuentes A, Martínez A, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol. 2020;183:729–37, http://dx.doi.org/10.1111/bjd.19327.
6. Restrepo-Arias VC, Arboleda J, López M, Soto A, Rincón L, Franco J. Autoinmunidad en pacientes pediátricos de una región de Colombia, tras un pico de SARS-CoV-2. Rev Colomb Reumatol. 2023, http://dx.doi.org/10.1016/j.rcreu.2023.08.001.
7. Montiel D, Quintana A, Villalba M, Olivares M, Rojas G, Rodríguez R. Manifestaciones autoinmunes en pacientes con COVID-19. Rev Parag Reumatol. 2021;7:34–40, http://dx.doi.org/10.18004/rpr/2021.07.02.34.
8. Lim SH, Ju HY, Han JH, Kim Y, Park Y, Lee S, et al. Autoimmune and autoinflammatory connective tissue disorders following COVID-19. JAMA Netw Open. 2023;6:e2336120, http://dx.doi.org/10.1001/jamanetworkopen.2023.36120.
9. Seeßle J, Oehmichen J, Gerhold M, von Euler M, Bönnemeier C, Koepke A, et al. Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. Clin Infect Dis. 2022;74:1191–8, http://dx.doi.org/10.1093/cid/ciab611.
10. Buonsenso D, Pata D, Chiaretti A, de Rose C, Valentini P, Esposito S. Preliminary evidence on long COVID in children. Acta Paediatr. 2021;110:2208–11, http://dx.doi.org/10.1111/apa.15870.
11. Liu F, Zhang Q, Zhou Y, Wang Y, Wang X, Zhu Z, et al. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol. 2020;18:2128–30.e2, http://dx.doi.org/10.1016/j.cgh.2020.04.040.
12. European Centre for Disease Prevention and Control. Increase in severe acute hepatitis cases of unknown aetiology in children. Available from: https://www.ecdc.europa.eu/en/increase-severe-acute-hepatitis-cases-unknown-aetiology-children.

Adriana Diaz-Maldonado[a,b]
[a] *Pediatric Rheumatology Program, Faculty of Medicine, Universidad El Bosque, Bogotá, Colombia*
[b] *Pediatric Rheumatology, Homi-Hospital Pediátrico La Misericordia, Instituto Roosevelt - Care for Kids, Bogotá, Colombia*
E-mail address: adriana.diazmaldonado@gmail.com

https://doi.org/10.1016/j.rcreue.2024.09.003