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COVID-19 in Children – A Review with a Focus on Pediatric Rheumatic Diseases

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Abstract

When compared with adults, children are less commonly symptomatic when having acute COVID-19 infection. It is yet not clear why COVID-19 appears to be less severe in children than in adults. Multiple factors might play a role such as colonization of upper respiratory tracts of children with various microorganisms which may complete with SARS-CoV2; more robust innate immune response; different expression of angiotensin-converting enzyme II receptor. However, some children have significant respiratory disease, and some children may develop postinfectious Multisystem Inflammatory Syndrome in Children (MIS-C). Among adult and pediatric patients with rheumatic disease receiving anti-rheumatic drugs, COVID-19 incidence rate is comparable with general populations and no increased risk of severe COVID-19 is being observed. There are few studies reporting COVID-19 in pediatric patients with rheumatic diseases. The control of the underlying rheumatic disease is of primary importance given the increased infection susceptibility carried by an active inflammatory status.

Keywords: *COVID-19; children; pediatric rheumatic diseases*

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), causing coronavirus disease 2019 (COVID-19), was first described in December 2019 in Wuhan, China. Soon after its initial description, COVID-19 rapidly spread across the world, and on March 11, 2020, the World Health Organization declared COVID-19 a global pandemic.[1] To date (17th Dec 2020) according to the European Centre for Disease Prevention and Control worldwide there are 71 554 018 confirmed cases of COVID-19, including 1 613 671 deaths.[2]

When compared with adults, children are less commonly symptomatic when having acute COVID-19 infection. In contrast to adults, most infected children appear to have a milder course and have better outcomes overall.[3] In concordance with the milder course of SARS–CoV-2 in children, the weekly rate of hospitalization due to COVID-19 among children under 18 years in 14 states in the United States is with a cumulative rate of 8 per 100,000 population.[4] The highest cumulative rate (24.8 8 per 100,000 population) is observed in children under 2 years of age.

In surveillance from various countries children typically account for up to 13 percent of laboratory-confirmed cases.[5-12] In a multicenter cohort of 582 European children under 18 years of age with laboratory-confirmed SARS-CoV-2 the age distribution was as follows : <1 month – 7 %; 1 month to 1 year – 22 %; 1 to 2 years – 10 %; 2 to 5 years – 11 %; 5 to 10 years – 16 %; above 10 years through 18 years – 34 % of the cases.[13] In a recently published article concerning school-aged children (aged 5-17 years) in United States, the average weekly incidence (cases per 100,000 children) of COVID-19 among adolescents aged 12-17 years was 37.4%, approximately twice that of children aged 5-11 years (19.0%).[14]

It is yet not clear why COVID-19 appears to be less severe in children than in adults. It is known that SARS-CoV-2 enters the cells after interactions between its transmembrane spike glycoprotein (S-protein) and specific cell receptors of angiotensin-converting enzyme II (ACE2).[15] It has been shown that the expression of this enzyme starts to increase in later childhood[16], and this may protect children from the most aggressive pattern of the infection.

Another possible explanation is the fact that children carry many different types of viruses in their respiratory tract, leading to viral interference and lower SARS-CoV-2 viral load. The less intense immune response observed in children is related to a lower chance of developing cytokine storm syndrome.

Material and Methods

To describe the characteristics of COVID-19 in children with a focus on pediatric rheumatic diseases. An electronic search in PubMed, using keywords COVID-19, children, pediatric rheumatology was performed.

Discussion

A systematic review of COVID-19 in children, among 7480 children with laboratory-confirmed COVID-19, predominantly from Italy, China, and the United States showed mainly mild (42.5%) and moderate (39.6%) signs of the infection.[17] Severe and critically ill children represented 2% and 0.6% of the total sample size, respectively. The estimated mortality of confirmed cases of SARS-CoV-2 infection was 0.08%. The most commonly described symptoms were fever (51.6%), cough (47.3%), and sore throat (17.9%). Extrarespiratory symptoms were mainly represented by diarrhea (9.7%), vomiting (7.2%), and fatigue (10.6%). The full blood cell count was unremarkable in most patients, with less than one fifth of them (17.1%) showing low white blood cell and lympho- or neutropenia (13.3%). Elevated inflammatory markers such as C-reactive protein and procalcitonin were shown by 31.1% of children.

However, some children have significant respiratory disease, and some children may develop a recently described hyperinflammatory syndrome. This new syndrome has been given preliminary case definitions, first from the UK Royal College of Paediatrics and Child Healthv (RCPCH) - (Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARSCoV-2 [PIMS-TS])[18] and subsequently by the Centre for Disease Control and Prevention (CDC) -(Multisystem Inflammatory Syndrome in Children, [MIS-C]).[19] The MIS-C case definition included a patient aged <21 years with fever (body temperature,>38.0°C) or report of subjective fever lasting at least 24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement (cardiovascular, dermatologic, gastrointestinal, hematologic, neurologic, renal, or respiratory) and no alternative plausible diagnoses, who tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR), serology, or antigen test or had exposure to COVID-19 within 4 weeks before the onset of symptoms of MIS-C.[20]

However, immune-compromised patients such as rheumatic disease which require immunosuppressive treatment strikingly are not found to be a risk factor for more severe disease course. Furthermore, withdrawal of medications may cause a flare of rheumatoid arthritis, which can lead to higher infection risk.[21]

In order to study the global effects of the pandemic on people with rheumatic diseases in March 2020 The COVID-19 Global Rheumatology Alliance (C19-GRA) was formed. The goal was to better understand the effects of the pandemic on people with rheumatic diseases and explore factors that might affect their risk of COVID-19 and severe disease. There have been several reports examining the prevalence of COVID-19 infection in patients with rheumatic diseases.[22] While most literature suggests similar prevalence of COVID-19 in the rheumatic disease population compared to the general population, one study indicated a slightly higher risk of mortality in individuals with rheumatic diseases.[23] Furthermore, similar to studies conducted in the general population, rheumatic disease patients with comorbidities also have higher odds of poor outcomes.[24]

Cases entered in C19-GRA by physicians in the United States from March 24 – August 26, 2020 comprised a total of 1,380 patients with rheumatic disease and COVID-19.[25] Overall, 36% of patients were hospitalized, and 6% died. Twenty-six percent of hospitalized patients required mechanical ventilation/ extracorporeal membrane oxygenation (ECMO). From the 1324 patients for whom there was data for race/ ethnicity information 504 were rheumatoid arthritis patients, 218 were systemic lupus patients, 124 were diagnosed with psoriatic arthritis, 59 patients were with axial spondyloarthritis and 99 with vasculitis. Underlying hypertension or cardiovascular disease was documented in 466, diabetes in 227 of them. Biological treatment was performed in 550 of them.

There are few studies reporting COVID-19 in pediatric patients with rheumatic diseases. Additionally, patients with rheumatic diseases are believed to be more likely to have viral infections like SARS-CoV-2, on the other hand antirheumatic drugs may have a protective and

therapeutic role in COVID-19 and children are more unlikely to have serious disease course. A recently published record from Turkey described 345 patients with juvenile idiopathic arthritis (JIA).[26] There were 8 patients with contact histories with confirmed COVID-19 cases. Six of them were on biological disease-modifying anti-rheumatic drugs (bDMARDs), one was on conventional DMARDs and the other one was being followed without treatment. In four of the contacted patients a SARS-CoV2 polymerase chain reaction test was performed with two of them being positive. Both of them were on bDMARDs. Both cases had cough, rhinorrhoea, anosmia and dyspnea. Additionally, one of them had fatigue, myalgia, arthralgia, headache, diarrhoea and nausea.

A survey-based study composed of 243 (58.7%) JIA patients, 109 (26.3%) children with autoinflammatory diseases, 51 (12.3%) with connective tissue diseases and 11 (2.7%) with vasculitis, found out that from the 9 patients who attended hospital because of COVID-19 evaluation due to exposure, SARS-CoV2 was identified in one patient with seronegative polyarticular JIA, previously prescribed methotrexate and receiving leflunomide during pandemic.[27]

In order to investigate the impact of COVID-19 on pediatric patients with rheumatic diseases treated with bDMARDs, with or without cDMARDS, a questionnaire was prepared and administered in pediatric rheumatology clinics in Milan, Lombardy.[28] The study cohort included 89 JIA patients, 5 patient with autoinflammatory diseases, 5 with chronic uveitis, 2 with recurrent pericarditis and 22 with other chronic rheumatic diseases. None of them were confirmed cases of COVID-19. Eight children presented mild respiratory symptoms, three of them were family members of adults suspected for COVID-19 infection. Preliminary experience supported the idea that patients with chronic diseases treated with bDMARDs do not seem to be at increased risk of respiratory or lifethreatening complications from SARS-CoV-2 compared with the general population. To support the idea that children with rheumatic diseases do not show an increased susceptibility to COVID-19 compared to healthy peers, Marino et al reported four patients diagnosed with JIA exposed to severe acute respiratory syndrome coronavirus 2 while receiving TNF inhibitors.[29] Biological therapy was discontinued in all patients for a median time of 8 weeks. None of the reported patients experienced severe COVID-19 manifestations.

Another study investigated the prevalence of COVID-19 in children within 404 patients with autoinflammatory diseases.[30] During pandemic, 375 (93%) were on colchicine treatment and 48 (11.8%) were receiving biologic treatment. Twenty-four out of 404 patients were admitted to hospital due to COVID-19 suspicion. Severe acute respiratory syndrome coronavirus-2 was identified through rhinopharyngeal swabs in seven patients, six of whom were only on colchicine treatment. Only one patient with no finding of any severe respiratory complications was hospitalized. All of seven patients recovered completely.

Conclusion

COVID-19 pandemic has a high mortality rate and a poorer outcome, particularly in elderly patients and individuals with comorbidities. There are very limited data about the infection rate and disease course in patients with rheumatic diseases and almost no data regarding pediatric rheumatology patients. And although the disease mostly has a mild course in children, a severe clinical manifestation related to SARS-CoV-2 infection in the face of MIS-C is increasingly being described. During this pandemic, the control of the underlying rheumatic disease is of primary importance given the increased infection susceptibility carried by an active inflammatory status.

References

[1] World Health Organization. Archived: WHO timeline - COVID-19. Available at: https://www.who.int/news-room/detail/ 27-04-2020-who-timeline-covid-19.

[2] European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/covid-19-pandemic

[3] Castagnoli R, Votto M, Licari A, et al. **Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review.** *JAMA* Pediatr. 2020;174(9):882–889. doi:10.1001/jamapediatrics.2020.1467

[4] Kim L, Whitaker M, O'Halloran A, et al. **Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020.** MMWR Morb Mortal Wkly Rep 2020; 69:1081.

[5] Wu Z, McGoogan JM. **Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention.** JAMA 2020; 323:1239.

[6] Statistica. **Distribution of Coronavirus cases in Italy as of December 2, 2020, by age group.** Available at: https://www.statista.com/statistics/1103023/coronavirus-cases-distribution-by-age-group-italy/.

[7] Age distribution of coronavirus (COVID-19) cases in South Korea as of November 20, 2020. https://www.statista.com/statistics/1102730/south-korea-coronavirus-cases-by-age/.

[8] Posfay-Barbe KM, Wagner N, Gauthey M, et al. **COVID-19 in Children and the Dynamics of Infection in Families.** Pediatrics 2020; 146.

[9] Docherty AB, Harrison EM, Green CA, et al. **Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.** BMJ 2020; 369: m1985.

[10] Stokes EK, Zambrano LD, Anderson KN, et al. **Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020.** MMWR Morb Mortal Wkly Rep 2020; 69:759.

[11] CDC COVID data tracker. Demographic trends of COVID-19 cases and deaths in the US reported to the CDC. Available at: https://www.cdc.gov/covid-data-tracker/index.html#demographics.

[12] American Academy of Pediatrics. Children and COVID-19: State-Level Data Report. Available at: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/.

[13] Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, et al . **COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study.** Lancet Child Adolesc Health. 2020 Sep;4(9):653-661.

[14] Leeb RT, Price S, Sliwa S, Kimball A, Szucs L, Caruso E, Godfred-Cato S, Lozier M. **COVID-19 Trends Among School-Aged Children - United States, March 1-September 19, 2020.** MMWR Morb Mortal Wkly Rep. 2020 Oct 2;69(39):1410-1415. doi: 10.15585/mmwr.mm6939e2. PMID: 33001869; PMCID: PMC7537558.

[15] Wang Y, Wang Y, Chen Y, Qin Q. **Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures**. J Med Virol. 2020;92:568–576. doi: 10.1002/jmv.25748.

[16] Muus C, Luecken MD, Eraslan G, et al (2020) **Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells.** bioRxiv 2020.04.19.049254. 10.1101/2020.04.19.049254.

[17] Liguoro I, Pilotto C, Bonanni M, et al. **SARS-COV-2 infection in children and newborns: a systematic review.** Eur J Pediatr 2020; 179:1029.

[18] Royal College of Paediatrics and Child Health. **Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19.**

[19] Centers for Disease Control and Prevention. **Emergency preparedness and response: multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19).** Health advisory (https://emergency .cdc .gov/han/ 2020/ han00432 .asp)

[20] Centers for Disease Control and Prevention. **Emergency preparedness and response: multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19).** Health advisory (https://emergency .cdc .gov/han/ 2020/ han00432 .asp)

[21] Favalli EG, Ingegnoli F, De Lucia O, et al. **COVID-19 infection and rheumatoid arthritis: Faraway, so close!** Autoimmun Rev. 2020 May;19(5):102523.

[22] Gianfrancesco M, Yazdany J, Robinson PC. **Epidemiology and outcomes of novel coronavirus 2019 in patients with immune-mediated inflammatory diseases.** Curr Opin Rheumatol. 2020 Sep;32(5):434-440. doi: 10.1097/BOR.0000000000000725. PMID: 32675715.

[23] Williamson EJ, Walker AJ, Bhaskaran K, et al. **Factors associated with COVID-19-related death using OpenSAFELY.** Nature. 2020 Aug;584(7821):430-436.

[24] Gianfrancesco M, Hyrich KL, Al-Adely S, et al. **Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry.** Ann Rheum Dis. 2020;79(7):859-66.

[25] Gianfrancesco MA, Leykina LA, Izadi Z, et al. **Race/ethnicity association with COVID-19 outcomes in rheumatic disease: Data from the COVID-19 Global Rheumatology Alliance Physician Registry.** Arthritis Rheumatol. 2020 Nov 3. doi: 10.1002/art.41567. Epub ahead of print. PMID: 33146001.

[26] Yildiz M, Haslak F, Adrovic A, et al. **The frequency and clinical course of COVID-19 infection in children with juvenile idiopathic arthritis.** Clin Exp Rheumatol. 2020 Nov-Dec;38(6):1271-1272. Epub 2020 Oct 18. PMID: 33124561.

[27] Koker O, Demirkan FG, Kayaalp G, et al. **Does immunosuppressive treatment entail an additional risk for children with rheumatic diseases? A survey-based study in the era of COVID-19.** *Rheumatol Int*. 2020;40(10):1613-1623. doi:10.1007/s00296-020-04663-9.

[28] Filocamo G, Minoia F, Carbogno S, et al. **Absence of severe complications from SARS-CoV-2 infection in children with rheumatic diseases treated with biologic drugs.** J Rheumatol. 2020 Apr 25:jrheum.200483. doi: 10.3899/jrheum.200483. Epub ahead of print. PMID: 32335512.

[29] Marino A, Romano M, Gattinara M, Cimaz R. **Patients with juvenile idiopathic arthritis on TNF inhibitors exposed to COVID-19 family members.** *Semin Arthritis Rheum*. 2020;50(6):1214-1215. doi:10.1016/j.semarthrit.2020.09.012.

[30] Haslak F, Yildiz M, Adrovic A, et al. **Management of childhood-onset autoinflammatory diseases during the COVID-19 pandemic.** *Rheumatol Int*. 2020;40(9):1423-1431. doi:10.1007/s00296-020-04645-x.

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