SARS-CoV-2 Infection in Children and Adolescents Living With HIV in Madrid

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Abstract: Multicenter study designed to describe epidemiologic and clinical characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive cases registered among children and adolescents living with HIV (CALWH). SARS-CoV-2 infection was confirmed in 13.3% of CALWH, with all patients presenting mild symptoms, and the outcome was good in all patients. None of the HIV- and antiretroviral treatment-related variables studied were associated with greater infection risk or could be considered protective.

Key Words: HIV, severe acute respiratory syndrome coronavirus 2, incidence, seroprevalence

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Since March 2020, when the new coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was declared a global pandemic, the virus has infected more than 250 million people all over the world, affecting vulnerable populations including children and adolescents living with HIV (CALWH). Coronavirus disease 2019 (COVID-19) in the general population is fairly well described, but the interaction between HIV infection in the severity and outcomes of COVID-19 remains little understood,[1,2] and data are sometimes contradictory.

Some evidence suggests that patients with advanced HIV disease (low CD4+ lymphocyte cell count), high viral load or those who are not on antiretroviral treatment (ART) are at higher risk of SARS-CoV-2 infection and associated complications.[1] However, other groups reported comparable rates of infection and complications in people living with HIV on ART, in good clinical and immunological conditions.[2] In a recent meta-analysis, Wang et al[3] found an increased risk of COVID-19 mortality in patients with HIV, but probably modulated by age, region and study design. Whether ART might play an antiviral role against SARS-CoV-2 is also a question to be answered.

Data are lacking regarding COVID-19 in CALWH. The incidence of SARS-CoV-2, risk of complication and rate of seroconversion among CALWH have not been reported. The aims of the study were to describe the epidemiological and clinical characteristics of the first SARS-CoV-2 positive cases registered among CALWH and to assess possible HIV- and ART-related risk or protective factors.

METHODS

A prospective multicenter study including CALWH followed up in the pediatric outpatient clinics of 5 hospitals in Madrid (Spain) between June 2020 and March 2021.

SARS-CoV-2 infection was considered confirmed when either a polymerase chain reaction (PCR) or rapid SARS-CoV-2 antigen test (RAT) in nasopharyngeal swab returned positive. PCR or RAT was performed throughout the study period on patients with symptoms and in those who reported contact with someone infected with SARS-CoV-2, following the indications of the Spanish Ministry for Health.

Blood samples for serological testing were collected after confirmed infection when patients attended routine outpatient appointments. Depending on the availability, various chemiluminescence serologic assays were used to determine SARS-CoV-2 IgG: COVID-19 VIRCLIA IgG-monotest, Vircell; ADVIA Centaur SARS-CoV-2 Total, Siemens; Alinity SARS-CoV-2 IgG II Quant, Abbott. All assays were performed according to the manufacturer's package insert.

Epidemiologic, immunovirological and ART data were collected from medical reports. Symptoms related to SARS-CoV-2 were actively collected during routine medical visits, by means of a specific questionnaire. Clinical and epidemiological characteristics, immunovirological data (undetectable plasma viral load: <50

copies/mL) and ART treatment (specifically, tenofovir alafenamide or tenofovir disoproxil fumarate exposure) were compared in patients with SARS-CoV-2 confirmed infection and those uninfected.

The study was approved by the ethical committees of the participating hospitals. For children under 18, a parent/guardian signed an informed consent. Informed assent forms were collected when applicable. Patients over 18 consented to participate themselves. Clinical symptom data were collected retrospectively for some patients to complete the gap between the beginning of the pandemic and the approval of the prospective study. Each patient received an anonymous number code to maintain confidentiality.

Median and interquartile ranges were used to describe continuous variables, and numbers and percentages to express categorical variables. To compare the characteristics of patients with confirmed SARS-CoV-2 infection and those without, Fisher's exact tests were used for categorical variables, and the Mann-Whitney test was used for continuous variables. A P value < 0.05 was considered statistically significant. Windows SPSS.20 (Madrid, Spain) was used for statistical analysis.

RESULTS

A total of 60 CALWH were studied during the study period. Among them, SARS-CoV-2 infection was confirmed in 8 (13.3%) patients: 7 diagnosed by PCR and 1 by RAT.

Median age of CALWH with SARS-CoV-2 infection was 19 years old (17–19.5 years), 62.5% were female. Three were Spanish (Caucasian) and 5 were born abroad (3 from Sub-Saharan area and 2 from Latin America). All were vertically infected, 5 patients were classified as CDC clinical stage A, 1 as stage B and 2 as stage C. By the time of SARS-CoV-2 infection, all were receiving ART. Plasma viral load was undetectable in 87.5% of patients, median CD4+ T-cell count was 671.5 cells/μL (582.5–817.5), and none had CD4+ T-cell count less than 500 cells/μL.

SARS-CoV-2 symptoms were reported by 7 (87.5%) of the 8 patients (Table 1). The most common clinical manifestation was upper respiratory tract infection (62.5%). None presented with multisystem inflammatory syndrome in children or required hospital admission or SARS-CoV-2 specific treatment.

TABLE 1. Characteristics of Children and Adolescents Coinfected: HIV and SARS-CoV-2

Total Patients Coinfected (HIV and SARS-CoV-2)	8
Epidemiologic characteristics	
Female	5 (62.5%)
Median age (yr)	19 (IQR: 17–19.5)
Born in Spain	3 (37.5%)
Clinical presentation	
Asymptomatic	1 (12.5%)
Symptomatic	7 (87.5%)
Upper respiratory tract infection symptoms	5 (62.5%)
Fever	4 (50%)
Anosmia and dysgeusia	3 (37.5%)
Asthenia	2 (25%)
Abdominal pain	1 (12.5%)
SARS-CoV-2 diagnosis (microbiologic test)	
Rapid antigen test (nasopharyngeal swab)	1 (12.5%)
PCR positive (nasopharyngeal swab)	7 (87.5%)
Epidemiologic status	
Contact with confirmed COVID-19 case (microbiological confirmation)	3 (37.5%)
Contact with someone with COVID-19 symptoms (no microbiological confirmation)	2 (25%)
No COVID-19 contact known	3 (27.3%)

IQR indicates interquartile range.

After confirmed infection, a SARS-CoV-2 IgG test was positive for 7 of 8 (87.5%) patients a median of 39 days (36.5–42.5 days) later. One asymptomatic patient with positive PCR, tested negative for SARS-CoV-2 IgG in 2 consecutive visits, at 1 and 6 months after the acute infection.

Patients with confirmed SARS-CoV-2 infection tended to be older than other CALWH, but the difference was not statistically significant [19 (17–19.5) vs. 13.5 (11–19) years old; $P = 0.12$). There were no differences in SARS-CoV-2 infection according to clinical stage (25% vs. 15% patients at CDC clinical stage C; $P = 0.79$), immunovirological status [CD4+ T-cell count: 671 (582–817) vs. 857 (666–982) cells/μL; $P = 0.14$], or tenofovir disoproxil fumarate/tenofovir alafenamide exposure (25% vs. 22%; $P = 0.80$).

DISCUSSION

In our study of 60 CALWH in Madrid, the clinical presentation and outcome of cases diagnosed with SARS-CoV-2 infection were comparable to that in the general pediatric population.[4] We found 13.3% of confirmed infection, with all patients presenting mild symptoms or asymptomatic. None required admission or specific antiviral treatment. The seroconversion rate after acute infection was 87.5%, which does not appear to be different in healthy children,[5] although the numbers are small. All positive PCR were performed before November 2021, so we assume that infections were probably caused by alpha and delta variants (no microbiological confirmation).

To our knowledge, this is one of the first series describing the incidence and clinical outcomes of SARS-CoV-2 infection in CALWH. Our results are reassuring, as data suggest an incidence that seems comparable to that of the pediatric Spanish population. All data were actively collected according to a structured questionnaire, reducing the potential for recall bias. Symptoms related to SARS-CoV-2 were predominately cough/rhinorrhea, followed by fever, similar to previously published data in healthy children[6,7] with a similar rate of complications. Despite the deleterious effects of HIV on the immune system of vertically infected patients, including chronic inflammation and immunoactivation,[8] our results do not suggest that HIV infection since birth in patients with good immunovirological control leads to a greater risk of SARS-CoV-2 morbidity.

Some studies have found higher mortality among HIV-COVID-19 coinfected people[3] and other groups described with low levels of CD4+ cell count as a risk factor of poor outcome.[9] In contrast, other studies found no relationship between COVID-19 incidence and outcomes and with virological or immunological factors.[10,11] We found no differences regarding CDC clinical stage, CD4+ T-cell count or viral load among CALWH with and without confirmed COVID-19. Patients with lower CD4+ T-cell counts tended to present a higher risk of SARS-CoV-2 infection, but the differences did not reach statistical significance. However, the small sample size of our cohort may have limited our ability to detect any difference. In addition, all children were receiving ART and had good immunovirological control, limiting our ability to assess the possible influence of immunosuppression or ART on the outcome.

Patients with SARS-CoV-2 infection tended to be older in our series. This finding might be explained by the fact that adolescents probably have more social interaction and riskier behavior (meeting friends, breaking restrictive social rules, or being less aware of SARS-CoV-2 infection risks), whereas younger children would have been more consciously protected against virus exposure by their parents.

CONCLUSIONS

In our cohort of perinatally CALWH, SARS-CoV-2 infection was confirmed in 13.3%. Symptoms did not appear to be different from those reported in the general population, and the outcome was good in all patients. None of the HIV- and ART-related variables studied were associated with greater infection risk. Larger, longitudinal studies are needed to describe the clinical course of SARS-CoV-2 infection among CALWH and the potential effect of ART on COVID-19.

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REFERENCES

1. Ambrosioni J, Blanco JL, Reyes-Urueña JM, et al.; COVID-19 in HIV Investigators. Overview of SARS-CoV-2 infection in adults living with HIV. *Lancet HIV*. 2021;8:e294–e305.
2. Gatechompol S, Avihingsanon A, Putcharoen O, et al. COVID-19 and HIV infection co-pandemics and their impact: a review of the literature. *AIDS Res Ther*. 2021;18:28.
3. Wang Y, Feng R, Xu J, et al. An updated meta-analysis on the association between HIV infection and COVID-19 mortality. *AIDS*. 2021;35:1875–1878.
4. Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. 2021; 175:316–317.
5. Tagarro A, Sanz-Santaeufemia FJ, Grasa C, et al.; EPICO-AEP Working Group. Dynamics of reverse transcription-polymerase chain reaction and serologic test results in children with SARS-CoV-2 infection. *J Pediatr*. 2022;241:126–132.e3.
6. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J*. 2020;39:469–477.
7. Ceano-Vivas M, Martín-Espín I, del Rosal T, et al. SARS-CoV-2 infection in ambulatory and hospitalised Spanish children. *Arch Dis Child*. 2020; 105:808–809.
8. Carrasco I, Tarancon-Diez L, Vázquez-Alejo E, et al.; Pediatric National AIDS Research Network of Spain (CoRISpe) integrated in the Translational Research Network in Pediatric Infectious Diseases (RITIP). Innate and adaptive abnormalities in youth with vertically acquired HIV through a multicentre cohort in Spain. *J Int AIDS Soc*. 2021;24:e25804.
9. Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with HIV and coronavirus disease-19. *Clin Infect Dis*. 2020;73:e1964–e1972.
10. Blanco JL; Casado JL; Blanco JR; et al. A prospective case-cohort study of COVID-19 in persons with HIV: COVID-19 study. [abstract 641]. In: Virtual conference on retroviruses and opportunistic infections; SFO, March 6 to 10, 2021.
11. Cabello A, Zamarro B, Nistal S, et al. COVID-19 in people living with HIV: a multicenter case-series study. *Int J Infect Dis*. 2021;102:310–315.

Current Abstracts

Cluster of Parechovirus Central Nervous System Infections in Young Infants—Tennessee, 2022

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Parechovirus (PeV) is a nonenveloped RNA virus of the Picornaviridae family. PeV infections range from mild, self-limiting gastroenteritis to severe sepsis-like disease and central nervous system (CNS) infection. Infants <3 months of age are disproportionately affected. PeV genotype 3 is responsible for the most severe cases, with a pattern of biannual cycle circulation that peaks during summer months. PeV infection is not a reportable disease. During April 12–May 24, 2022, 23 previously healthy infants 5 days–3 months old were admitted to a Tennessee children's hospital for human PeV meningoencephalitis. The Tennessee Department of Health was notified and an assessment was conducted to better understand this unusually large cluster of infections.

At this children's hospital, a lumbar puncture is performed as part of sepsis evaluation for all infants <1 month old and for older infants when clinically indicated. Cerebrospinal fluid (CSF) testing includes a multiplex molecular panel (BioFire FilmArray Meningitis/Encephalitis Panel, bioMerieux) for all infants ≤3 months old and for patients >3 months of age if the CSF white blood cell (WBC) count is >5 cells per high power field. For this investigation, a comprehensive review of electronic health records was conducted to assess demographic characteristics, social history, signs and symptoms at admission, laboratory test results, and treatment course of all patients in whom PeV was detected by the multiplex molecular panel during the cluster period.

Median age of the patients was 24 days; 13 (57%) were female and 10 (43%) were male. Five patients were preterm (28–36 weeks' gestation). Signs and symptoms included fever, fussiness, and poor feeding. Most patients became symptomatic in the community (22, 96%); 1 preterm infant became symptomatic while in the neonatal intensive care unit (NICU). One (4%) patient attended a child care facility, and 16 (70%) had siblings at home or were exposed to other children.

Leukopenia was detected in only 4 (17%) patients. All but one of the infants were admitted to the hospital; 4 (17%) infants developed severe disease that required treatment in the NICU. Brain magnetic resonance imaging was performed in 4 severely ill NICU patients, which detected diffusion within the white matter consistent with typical PeV meningoencephalitis in all of these patients.

Antibiotics were initially prescribed for the 23 patients but were discontinued for 13 (57%) within 24 hours of detection of PeV. Mean hospital stay was 4.5 days (range, 1–26 days). Twenty-one (91.3%) patients recovered without complications. One patient was scheduled for a 6-month follow-up for possible late onset hearing loss and hypercoagulation evaluation. One patient experienced persistent seizures and was anticipated to experience severe developmental delay.

Comment: The multiplex molecular panel was introduced at the children's hospital in May 2018. Nineteen cases were detected over 5 months in 2018, likely representing a baseline incidence of PeV CNS infections. Seven cases of PeV were detected in 2019–2021. The absence of a biennial peak in 2020 may reflect social isolation during the COVID-19 pandemic, suggesting that PeV transmission is closely associated with social activity. Twenty-nine cases, including the 23 cases described in this report, were detected at the children's hospital within a 6-week period in 2022. This peak in infections might be a result of relaxation of COVID-19 isolation measures, consistent with increased prevalence of other viruses (e.g., respiratory syncytial virus). When PeV is circulating, clinicians should consider testing for PeV in young infants, including those with normal CSF parameters. The rapid detection of PeV in CSF by multiplex molecular panels can limit antibiotic administration and improve patient management.