COVID-19 and rhinovirus in pediatric: are there differences in clinical presentation and outcomes?

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Abstract

The dynamic of SARS-CoV-2 and other respiratory virus in children and adolescents is relevant in clinical context. There are few studies comparing clinical course in COVID-19 (coronavirus disease) and other respiratory virus in pediatric patients. The aim of this study was to compare demographics and clinical features, exams abnormalities, and outcomes in SARS-CoV-2 and other respiratory virus infections in a pediatric population. This was a single-center prospective study, between April 17 to September 30, 2020. We evaluated 76 pediatric COVID-19 and 157 other respiratory virus infections. Rhinovirus occurred in 132/157(84%). COVID-19 patients were significantly older, had more fever (69% versus 50%; p=0.01), pneumonia (22% versus 5%; p<0.01), myalgia (29% versus 8%; p=0.001), headache (31% versus 14%; p=0.01) and worse outcomes than those with other respiratory virus infections. Our data emphasizes differences in clinical presentation and outcomes between pediatric COVID-19 and rhinovirus infections.

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Abstract: The dynamic of SARS-CoV-2 and other respiratory virus in children and adolescents is relevant in clinical context. There are few studies comparing clinical course in COVID-19 (coronavirus disease) and other respiratory virus in pediatric patients. The aim of this study was to compare demographics and clinical features, exams abnormalities, and outcomes in SARS-CoV-2 and other respiratory virus infections in a pediatric population. This was a single-center prospective study, between April 17 to September 30, 2020. We evaluated 76 pediatric COVID-19 and 157 other respiratory virus infections. Rhinovirus occurred in 132/157(84%). COVID-19 patients were significantly older, had more fever (69% versus 50%; p=0.01), pneumonia (22% versus 5%; p<0.01), myalgia (29% versus 8%; p=0.001), headache (31% versus 14%; p=0.01) and worse outcomes than those with other respiratory virus infections. Our data emphasizes differences in clinical presentation and outcomes between pediatric COVID-19 and rhinovirus infections.

Background

Studies comparing SARS-CoV-2 and other respiratory viral infections in adults have been widely studied, however pediatric data is scarce. This may be due to broad social distancing and school closure in pediatric populations during coronavirus disease 2019 (COVID-19) pandemic.(1)

Trenholme et al. from New Zealand demonstrated reduction in hospitalization rates in infants < 2 years with lower respiratory tract virus infections in 2020 compared to the 6 years prior the exception of rhinovirus, remained stable.(1) Zhang et al. showed a decline in influenza virus from 14.9% (March 2020) to 1.86% (April 2020).(2)

Studies show pediatric coinfection rates of SARS-CoV-2 infection and other respiratory pathogens (ORP) ranging from 13.2% to 51.4%. (2,3)

Therefore, the objective of the present study was to compare SARS-CoV-2 infection and other respiratory tract virus infections in a pediatric population assessing demographics, comorbidities, clinical features, laboratory data and outcomes.

Methods

Study design

A single-center prospective study was conducted from April 17, 2020 to September 30, 2020. Visits occurred at Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP) in São Paulo, Brazil. The Ethics Committee of our Institution approve this study and written consent assignment was obtained from each patient before inclusion in the study.

We collected 1,566 respiratory samples from 1,044 patients younger than 18 years to assess SARS-CoV-2 infection. Of these, 919 were analyzed further in search of other respiratory pathogens (ORP). The samples were collected in pediatric patients with the following clinical findings: flu-like syndrome in high-risk children (<5 years or underlying conditions), fever without a source, severe acute respiratory syndrome (SARS), complete or incomplete Kawasaki Disease (KD), KD shock syndrome, MAS (macrophage-activating syndrome), gastrointestinal or neurological signs/symptoms.(4)

We included only patients with laboratory confirmed COVID-19 or ORP. In patients with high suspicion of COVID-19 but negative RT-PCR (real-time reverse transcription-polymerase chain reaction), serology was collected within 14 days of symptom onset. We excluded pre-surgical screenings or presence of bacterial coinfection.

Patients were divided in two groups: (a) Group 1 - laboratory confirmed pediatric COVID-19 patients without coinfection of ORP; (b) Group 2 - other respiratory virus infections, excluding SARS-CoV-2.

Data collection

Data was systematically reviewed by patient's records: (a) demographics: age, sex, duration of signs/symptoms before diagnosis; (b) chronic conditions: pulmonary, neuropathies, cardiopathies, diabetes mellitus, systemic arterial hypertension, immunocompromising diseases [primary immunodeficiency, solid organ transplantation, hematopoietic stem cell transplant (HSCT), malignancies, chronic kidney disease, autoimmune diseases], and the use of immunosuppressive agent; (c) clinical features: fever, duration of fever, nasal discharge, sneezing, coughing, dyspnea, anosmia, pneumonia, myalgia, headache, conjunctivitis, rash, diarrhea, vomiting, abdominal, pain, neurological symptoms, seizure, SARS, hypoxemia and arterial hypotension; (d) laboratory parameters: hemoglobin concentration, leucocyte, lymphocyte and thrombocyte counts, C-reactive protein, fibrinogen, D-dimer, ferritin, lactate dehydrogenase; (e) radiological exams: thoracic radiography and computer tomography; (f) treatments: supplementary oxygen, antibiotics, oseltamivir, intravenous immunoglobulin, enoxaparin, aspirin, systemic glucocorticoids and dialysis; (g) and outcomes: hospitalization, admission in pediatric intensive care unit (PICU), duration of hospitalization, mechanical ventilation, vasoactive agents, shock, cardiac abnormalities, and death.

Laboratorial methods

Respiratory samples (nasopharynx swab and/or tracheal aspirates) were submitted to molecular analysis at the Molecular Biology Laboratory HCFMUSP: Fast-track Diagnostics® (Panel 21), detects 21 respiratory pathogens: adenovirus, bocavirus, coronavirus (229E; HKU1; NL63; OC43), human rhinovirus/enterovirus, influenza virus A (H1N1, H3N2, Influenza A H1N1/2009), influenza virus B, Influenza virus C, metapneumovirus A e B, Mycoplasma pneumoniae, parainfluenza virus (1-4), parechovirus, respiratory syncytial virus (RSV) A and B.(5) RT-PCR for SARS-CoV-2 analysis was performed, according to the Charité University protocol.(6)

Serology was performed at the HCFMUSP Immunology Laboratory by imunocromatographic test (SARS-CoV-2 antibody test® WONDFO) or by enzyme linked immunosorbent assay (LIAISON® XL | DiaSorin).(4)

Statistical analysis

For continuous variables Mann-Whitney test and Student's t-test were applied and results were presented by median (minimum and maximum values) or mean ± standard deviation, as appropriated. For categorical variables Chi-square test and Fisher´s exact tests were used. We considered statistical significance with $p<0.05$. The IBM-SPSS-22 software was applied in statistical analyses.

Results

SARS-CoV-2 infection was detected in 91 patients (77 detected by RT-PCR and 14 by serology). Eight pediatric COVID-19 cases were excluded for bacterial coinfection. Panel 21 was performed in 56 laboratory

confirmed COVID-19 patients, seven patients had coinfection with rhinovirus. Respiratory viruses were detected in 195 patients and 31 were excluded for bacterial coinfection.

Therefore, 76 patients were included in Group 1; 157 patients in Group 2. Table 1 present demographical and clinical features of patients in Group 1 and 2.

Patients with underlying conditions were in two groups and were described in Table 2.

The ORP identified in Group 2 were: human rhinovirus/enterovirus, n=132/157 (84.0%); adenovirus, n= 18/157 (11,5%); bocavirus n=8/157 (5%); RSV, n=6/157 (3.8%); other coronavirus n=3/157 (1.9%); influenza, parainfluenza and parechovirus, n=2/157 (1.3%) each one. 17/157 (10,8%) had viral coinfections, of which 94,1% (16/17) was attributed to rhinovirus/enterovirus.

Laboratory exams and radiological abnormalities frequency of two groups were exhibited in table 3.

In Group 1, nine patients had multisystem inflammatory syndrome in children (MIS-C), of which none presented viral coinfection. 50% of all deaths (4/8) occurred in MIS-C patients. Table 4 show outcomes and treatment in two groups.

Further analysis between SARS CoV-2 infection compared to only rhinovirus showed that the last group were significantly younger [135 (1-215) months vs 63 (2-216 months of age); p=0.001]; presented higher frequency of coughing [30/74 (41%) vs 73/123 (59%); p=0.01], lower frequency of fever [52/76 (69%) vs 62/130 (48%); p=0.01] and shorter duration of fever [median of 2 (0-15) vs 1 (0-12) days; p=0.02] compared to the former group. On the other hand, SARS-CoV-2 group presented the following signs/symptoms more frequently: anosmia [7/48 (15%) vs 2/85 (2%); p=0.01]; pneumonia [17/76 (22%) vs 6/130 (5%); p<0.001]; myalgia [18/62 (29%) vs 7/88 (8%); p=0.001]; headache [18/58 (31%) vs 14/91 (15%); p=0.03] and rash [7/74 (10%) vs 2/120 (2%); p=0.03]. SARS-CoV-2 group also presented with higher ferritin levels [median 201 (15-35,976) vs 85 (18-3,837); p=0.002] and lower leucocyte count [median 6,470 (430-25,890) vs 8,630 (170-21,120); p=0.01]. Radiographic abnormalities were found more frequently in SARS-CoV-2 group [25/49 (51%) vs 20/67 (30%); p=0.03]. Use of antibiotics [40/76 (53%) vs 49/131 (38%); p=0.04], oseltamivir [20/76 (26%) vs 13/131 (10%); p=0.003], intravenous immunoglobulin [7/75 (9%) vs 2/131 (2%); p=0.01] and enoxaparin [7/76 (9%) vs 1/130 (1%); p=0.004] were more frequent in SARS-CoV-2 group. Furthermore, SARS-CoV-2 group presented with poorer outcomes: higher rates of hospitalization [51/76 (67%) vs 58/131 (44%); p=0.002], PICU admission [18/76 (24%) vs 5/130 (4%); p<0,001], need of oxygen [23/76 (30%) vs 19/131 (15%); p=0.01], shock [8/76 (11%) vs 3/131 (2%); p=0.02], mechanical ventilation [9/76 (12%) vs 3/131 (2%); p=0.01], use of vasoactive agents [5/76 (7%) vs 1/131 (1%); p=0.03] and cardiac abnormalities [10/76 (13%) vs 1/130 (1%); p<0.001].

There were no statistically significant differences between seven cases of rhinovius/enterovirus and SARS-CoV-2 coinfected patients and those in Group 1 (p>0.05).

Discussion

In our study, patients with COVID-19 were older than those with ORP infections. This findings were similar to the results of Melé et al.: median age 16.9 years old for SARS-CoV-2 versus 3.5 years for non-SARS-CoV-2(p=0.004).(7)

We also demonstrated that fever, headache, anosmia, dysgeusia, myalgia and rash were more prevalent in the SARS-CoV-2 group, while cough was more frequent in Group 2. Melé et al., on the other hand indicated similar clinical findings between groups.(7)

Radiographic examinations were more often altered in the SARS-CoV-2 group in our study, which contraposed the findings of the Spanish team, where radiographic results were similar between groups.(7)

Considering outcomes and greater demand of clinical support, we found that pediatric COVID-19 was more severe when compared to other virus. In the Spanish study, COVID-19 patients also needed more cardiovascular support.(7)

However, rhinovirus comprises 84% of all respiratory virus excluding SARS-CoV-2 in our study. Due to this selection bias inherent to the world's epidemiological status, we are unable to suggest that these differences are applicable to other respiratory viruses such as influenza or RSV.

Trenholme et al. reported stable rhinovirus infection rates in 2020, as opposed to reduced RSV and influenza infection rates. In agreement, we showed that the rhinovirus seems to be the main circulating virus besides SARS-CoV-2 in 2020, so much so that rhinovirus was the only virus to present as a coinfection with SARS-CoV-2.(1) Zhang et al. showed a Rhinovirus/SARS-CoV-2 coinfection rate of 23,3%.(2)

Comparing SARS-CoV-2 and influenza infection, Piroth et al. observed that in the pediatric population: (a) influenza infection was more significantly frequent than COVID-19, (b) COVID-19 patients had worse outcomes (higher PICU admission and in-hospital mortality), which confirmed with our findings; and (c) COVID-19 patients had more underlying conditions (hypertension, respiratory disease, heart failure and obesity) than patients with influenza.(8)

Alvares compared children with solely SARS-CoV-2 infection versus SARS-CoV-2/RSV coinfection, and demonstrated longer hospitalizations in the coinfection group.(9) Here, coinfection rates of SARS-CoV-2 were low, likewise reported in other studies.(2,7,10)

The limitations to our study were selection bias and we only assessed patients from a single high complexity center, mainly including pediatric chronic conditions, and with a limited time frame.

Our data reinforces differences in clinical presentation, laboratory abnormalities and outcomes between pediatric COVID-19 and rhinovirus infections. Further studies are required to better understand SARS-CoV-2 and its role within the myriad of pediatric respiratory infections.

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