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BRIEF COMMUNICATION

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SARS-CoV-2 and rhinovirus infections: are there differences in clinical presentation, laboratory abnormalities, and outcomes in the pediatric population?

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ABSTRACT

This study aims to assess COVID-19 and other respiratory viruses in pediatric patients. Between April 17 and September 30, 2020, we collected 1,566 respiratory samples from 1,044 symptomatic patients who were younger than 18 years old to assess SARS-CoV-2 infection. Of these, 919 were analyzed for other respiratory pathogens (ORP). Patients with laboratory-confirmed COVID-19 or ORP were included. We evaluated 76 pediatric COVID-19 infections and 157 other respiratory virus infections. Rhinovirus occurred in 132/157 (84%). COVID-19 patients who were significantly older, had more fevers, headaches and pneumonia than those with ORP. The median white blood cell count was lower in patients with SARS-CoV-2 than in those with ORP (6,470 versus 8,170; p=0.02). COVID-19 patients had significantly worse symptoms than those with ORP.

KEYWORDS: Child. COVID-19. SARS-CoV-2. Rhinovirus.

BACKGROUND

The impacts of SARS-CoV-2 and other respiratory viral infections on adults have been widely studied, but pediatric data are scarce. This may be due to broad social distancing as a result of school closures during the coronavirus pandemic in 2019 (COVID-19).

Trenholme *et al.*[1] from New Zealand demonstrated a reduction in hospitalization rates in infants under 2 years old with lower respiratory tract virus infections in 2020 compared to the 6 years prior, except for rhinovirus, which remained stable. According to Zhang *et al.*[2], the influenza virus decreased from 14.9% in March 2020 to 1.86% in April 2020. Studies show pediatric coinfection rates of SARS-CoV-2 and other respiratory pathogens (ORP) ranging from 13.2% to 51.4%[2,3].

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

MATERIALS AND METHODS

Study design

A single-center prospective study was conducted from April 17, 2020 to September 30, 2020. Visits occurred at the Hospital das Clinicas da Faculdade de Medicina da USP (HCFMUSP) in Sao Paulo, Brazil. The Ethics Committee of our institution approved this study (CAAE 30344420.6.0000.0008). Informed consent was obtained from the parents or legal guardians of the patients. Regarding children over seven years old or adolescents, a consent term was provided in addition to the consent obtained from the parents.

We collected 1,566 respiratory samples from 1,044 patients younger than 18 years old to assess the SARS-CoV-2 infection. Of these, 919 were analyzed further in search of other respiratory pathogens (ORP). The samples were collected from pediatric patients with the following clinical findings: a flu-like syndrome in high-risk children (under 5 years old or with underlying conditions), fever with no source, severe acute respiratory syndrome (SARS), complete or incomplete Kawasaki Disease (KD), KD shock syndrome, MAS (macrophage activation syndrome), and gastrointestinal or neurological signs/symptoms[4].

We included only patients with laboratory-confirmed COVID-19 or ORP. In patients with a high suspicion of COVID-19 but a 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 the presence of bacterial coinfections.

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

Data collection

Data were systematically reviewed through patients' medical records: (a) demographics: age, gender and duration of signs/symptoms prior to 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 use of immunosuppressive agents; (c) clinical features: fever, fever duration, 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, aspartate aminotransferase, alanine aminotransferase, blood urea, serum creatinine, triglycerides, creatine kinase, and troponin T; (e) radiological exams: thoracic radiography and computer tomography; (f) treatments: supplemental oxygen, antibiotics, oseltamivir, intravenous immunoglobulin, enoxaparin, aspirin, systemic glucocorticoids, and dialysis; (g) and outcomes: hospitalization, admission to a pediatric intensive care unit (PICU), duration of hospitalization and PICU, mechanical ventilation, vasoactive agents, shock, cardiac abnormalities and death.

Laboratory methods

Respiratory samples (nasopharynx swab and/or tracheal aspirates) were submitted for molecular analysis at the Molecular Biology Laboratory HCFMUSP: the Fast-track Diagnostics Respiratory Pathogens 21 Assay® (Siemens Healthineers, Erlangen, Germany) 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 immunochromatographic test, Wondfo SARS-CoV-2 antibody test® (Wondfo Biotech, Guangzhou, China), or by anti-SARS-CoV-2 enzyme-linked immunosorbent assay, LIAISON®SARS-CoV-2 IgG kit (DiaSorin, Saluggia, Italy)[7,8].

Statistical analysis

For continuous variables, Mann-Whitney's test and Student's t-test were applied and results were presented by median (minimum and maximum values) or mean ± standard deviation, as appropriate. For categorical variables, the Chi-square test and Fisher's exact test were used. We considered statistical significance to be $p < 0.05$. The IBM-SPSS statistical software (version 22, IBM Corporation, Armonk, NY, USA) was applied in the 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 on 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 and 157 in Group 2 (Figure 1).

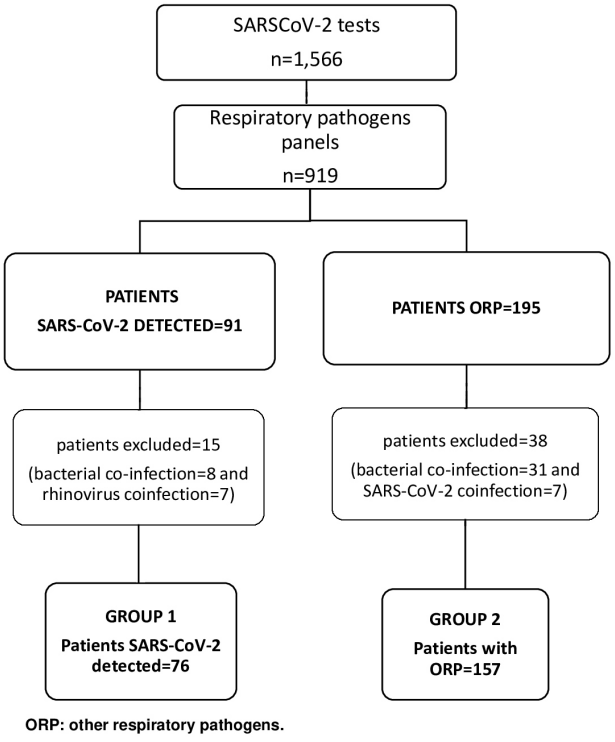

Figure 1 - Description of the samples from pediatric patients with clinical findings (Groups 1 and 2) from April 17 to September 30, 2020. ORP = other respiratory pathogens.

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.

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; 17/157 (10.8%) had viral coinfections, of which 94.1% (16/17) were attributed to rhinovirus/enterovirus. Table 1 presents the demographic features, clinical presentation and underlying conditions of patients in Groups 1 and 2. Laboratory tests, radiographic abnormalities, treatment and outcomes of patients in Groups 1 and 2 are described in Table 2.

Further analysis between SARS CoV-2 infection compared to rhinovirus showed that the last group was significantly younger [135 (1–215) months vs. 63 (2–216 months of age); p = 0.001]; presented a 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, the 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 the 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 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 the seven cases of rhinovirus/enterovirus and SARS-CoV-2 coinfected patients and those in Group 1 (p>0.05).

DISCUSSION

During the COVID-19 pandemic in 2020, rates of viral infections in the pediatric population were low worldwide[1,2]. The same pattern was observed in our study. Despite the SARS-CoV-2 outbreak, rhinovirus was the most frequently detected respiratory virus in the studied population. In this specific clinical scenario, we will mainly discuss some striking differences between SARS-CoV-2 and rhinovirus infections. Due to differences in management, the distinction between rhinovirus and SARS-CoV-2 is of clinical importance.

In our study, patients with COVID-19 were older than those with ORP infections. This finding was similar to the

Table 1 - Demographic data, clinical presentation and chronic conditions of laboratory-confirmed pediatric COVID-19 *versus* other respiratory virus infections.

Variables	SARS CoV-2 (n=76)	Other respiratory virus (n=157)	p-value
Demographic data			
Current age (months)	135 (1–215)	63 (2–216)	**0.001**[$]
Age < 5 years	23 (30)	72 (46)	**0.02**
Duration of signs/symptoms before diagnosis (days)	3 (0–21)	3 (0–13)	0.89
Male sex	41 (54)	83 (53)	0.90
Clinical presentation			
Fever	52/76 (69)	77/155 (50)	**0.01**[&]
Fever duration (days)	2 (0–15)	1 (0–12)	0.07[$]
Nasal discharge	30/75 (40)	79/149 (53)	0.09[&]
Sneezing	14/74 (19)	25/140 (18)	0.85[&]
Cough	30/74 (41)	84/146 (58)	**0.02**[&]
Dyspnea	25/74 (34)	50/151 (33)	1.0[&]
Anosmia	7/48 (14)	3/95 (3)	**0.03**[&]
Dysgeusia	5/41 (12)	2/95 (2)	**0.03**
Pneumonia	17/76 (22)	8/155 (5)	**<0.01**[&]
Myalgia	18/62 (29)	8/98 (8)	**0.001**
Headache	18/58 (31)	14/100 (14)	**0.01**[&]
Conjunctivitis	4/68 (6)	4/118 (3)	0.47[&]
Cutaneous rash	7/74 (10)	3/144 (2)	**0.03**[&]
Diarrhea, vomiting and/or abdominal pain	23/75 (31)	33/148 (22)	0.19[&]
Neurological (seizure)	6/75(8)	13/152 (9)	1.0[&]
Pediatric SARS	13/75 (17)	16/155 (10)	0.14[&]
Hypoxemia	18/75 (24)	29/154 (19)	0.39[&]
Arterial hypotension	8/75 (11)	4/154 (3)	**0.02**[&]
Chronic conditions	56/76 (74)	135/157 (86)	**0.03**[&]
Previously healthy	20/76 (26)	22/157 (14)	**0.03**[&]
Pulmonary	8/76 (11)	23/157 (15)	0.42[&]
Neuropathy	8/76 (11)	19/157 (12)	0.83[&]
Cardiopathy	5/76 (7)	10/157 (6)	1.0[&]
Diabetes	1/76 (1)	5/157 (3)	0.67[&]
Systemic arterial hypertension	12/76(16)	11/157 (7)	0.06[&]
Immunocompromising diseases	30/76 (40)	57/157 (36)	0.66[&]
Primary immunodeficiency	1/76 (1)	6/157 (4)	0.43[&]
Solid organ transplantation or HSCT	4/76 (5)	15/157 (10)	0.32[&]
Malignancy	17/76 (22)	31/157 (20)	0.73[&]
Chronic kidney disease (stages 1-5)	5/76(7)	7/157 (5)	0.53[&]
Autoimmune conditions	7/76 (9)	8/157 (5)	0.26[&]
Immunosuppressive use	26/76 (34)	46/157 (29)	0.45[&]

Results are presented in n (%), median (minimum-maximum values) or mean ± standard deviation and n (%). SARS = severe acute respiratory syndrome; HSCT = hematopoietic stem cell transplantation; $ = Mann-Whitney's U-test; & = Fisher's exact test.

Table 2 - Exams, outcomes and therapies of laboratory-confirmed pediatric COVID-19 *versus* other respiratory virus infections.

Variables	SARS CoV-2 (n=76)	Other respiratory virus (n=157)	p-value
Hematological parameters			
Hemoglobin (g/dL)	12 (5–15)	12 (7–17)	0.41[$]
Leucocyte (count/mm^3)	6,470 (430–25,890)	8,170 (90–27,350)	**0.02[$]**
Lymphocyte (count/mm^3)	1,630 (0–17,860)	1,970 (0–19,000)	0.25[$]
Thrombocyte (count/mm^3)	219,000 (13,000–644,000)	229,500 (6,000–1,630,000)	0.39[$]
Inflammatory markers			
C-reactive protein (mg/L)	11 (0.3–407)	13 (0.30–332)	0.73[$]
Fibrinogen (mg/dL)	306 (101–842)	292 (53–678)	0.38[$]
D-dimer (ng/mL)	1,251 (190–95,040)	755 (190–42,660)	0.39
Ferritin (ng/mL)	201 (15–35,976)	93 (18–3,837)	**0.01**
Other exams			
Lactate dehydrogenase (U/L)	294 (130–4,476)	295 (175–718)	0.77
Aspartate aminotransferase (U/L)	30 (10–2,002)	34 (16–496)	0.13
Alanine aminotransferase (U/L)	21 (5–560)	23 (9–572)	0.26
Blood urea (mg/dL)	21 (1–186)	25 (4–79)	0.23
Serum creatinine (mg/dL)	0.43 (0.03–26)	0.42 (0.17–17)	0.62
Triglycerides (mg/dL)	156 (51–308)	117 (32–830)	0.47
CK (U/L)	86 (13–2,291)	102 (35–725)	0.13
Troponin T (ng/mL)	0.01 (0.003–1.05)	0.007 (0.003–0.05)	0.08
Lung radiographic and CT imaging			
Pulmonary X-ray abnormalities	25/49 (51)	24/80 (30)	**0.03**
Pulmonary CT abnormalities	14/21 (67)	2/9 (22)	**0.04**
Outcomes			
Hospitalization	51/76 (67)	73/156 (47)	**0.01**
Duration of hospitalization (days)	6 (1–67)	6 (1–99)	0.54
PICU admission	18/76 (24)	6/155 (4)	**0.000**
Period in PICU (days)	5 (1–46)	9 (3–21)	0.38
Mechanical ventilation	9/76 (12)	4/156 (3)	**0.01**
Vasoactive agents	5/76 (7)	1/156 (1)	**0.02**
Shock	8/76 (11)	4/156 (3)	**0.02**
Cardiac abnormalities	10/76 (13)	1/155 (1)	**<0.01**
Death	5/76 (5)	1/156 (1)	0.04
Therapies			
Oxygen	23/76 (30)	22/156 (14)	**0.01**
Antibiotic	40/76 (53)	63/156 (40)	0.09
Oseltamivir	20/76 (26)	17/156 (11)	**0.004**
Intravenous immunoglobulin	7/75 (9)	2/156 (1)	**0.01**
Enoxaparin	7/76 (9)	1/155 (1)	**0.002**
Aspirin	4/76 (5)	1/156 (1)	**0.04**
Systemic glucocorticoid	12/76 (16)	21/156 (14)	0.69
Dialysis for acute renal replacement therapy	2/76 (3)	1/154 (1)	0.25

Results are presented in n (%), median (minimum–maximum values) or mean ± standard deviation and n (%); CK = creatine phosphokinase; CT = computer tomography; PICU = pediatric intensive care unit; $ = Mann-Whitney's U-test; & = Fisher's exact test. Normal reference values: fibrinogen (200–393 mg/dL), D-dimer (< 500 ng/mL), ferritin (36–391 ng/mL), lactate dehydrogenase (120–300 U/L), aspartate aminotransferase (< 37 U/L), alanine aminotransferase (< 41 U/L), blood urea (10–50 mg/dL), serum creatinine (< 1.04 mg/dL), triglycerides (< 90 mg/dL), CK (< 190 U/L) and troponin (< 0.014 ng/mL).

results of Melé *et al.*[9]: the median age was 16.9 years old for SARS-CoV-2 versus 3.5 years for non-SARS-CoV-2 (p = 0.004). We also demonstrated that fever, headache, anosmia, dysgeusia, myalgia, and rash were more common in the SARS-CoV-2 group, while cough was more frequent in Group 2. On the other hand, Melé *et al.*[9] indicated similar clinical findings between the groups.

Considering the outcomes and the greater demand for clinical support, we found that pediatric COVID-19 was more severe when compared to other respiratory virus infections. In the Spanish study, COVID-19 patients also needed more cardiovascular support[9]. In our study, radiographic examinations were more often altered in the SARS-CoV-2 group, which contradicted the findings of the Spanish team, whose radiographic results were similar between the groups[9].

Trenholme *et al.*[1] reported stable rhinovirus infection rates in 2020, as opposed to reduced RSV and influenza infection rates. Accordingly, we showed that the rhinovirus seems to be the main circulating virus in 2020, besides SARS-CoV-2, to such a degree that the rhinovirus was the only virus to be present as a coinfection with SARS-CoV-2. According to Zhang *et al.*[2] the rate of rhinovirus/SARS-CoV-2 coinfection was 23.3%.

Rhinovirus comprises 84% of all respiratory viruses, 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 apply to other respiratory viruses such as influenza or RSV.

Comparing SARS-CoV-2 and influenza infection, Piroth *et al.*[10] 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 was confirmed by our findings; and (c) COVID-19 patients had more underlying conditions (hypertension, respiratory disease, heart failure, and obesity) than patients with influenza.

Alvares[11] compared children with solely SARS-CoV-2 infection versus SARS-CoV-2/RSV coinfection and demonstrated longer hospitalizations in the coinfection group. Here, coinfection rates of SARS-CoV-2 were low, as reported in other studies[2,9,12].

The limitations of our study were selection bias and the fact that we only evaluated patients from a single high-complexity center, primarily for pediatric chronic conditions, over a short time.

Our data reinforce the 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 in the myriad of pediatric respiratory infections.

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AUTHORS' CONTRIBUTIONS

All the authors contributed substantially to the conception and design of the study and the analysis and interpretation of the data. All authors revised the work critically and approved the definitive version.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

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