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Oral manifestations in hospitalized children with COVID-19

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Abstract: As the pandemic progressed, the incidence of viruses among children also increased. This study investigates the presence of oral lesions in hospitalized children by analyzing data collected from medical records of infants seen at the pediatric Infectious disease unit at the General Hospital of the University of Pernambuco, Recife, Brazil, from March to August 2020. This study includes children aged 0 to 12 years diagnosed with severe symptoms of COVID-19. The data describe the frequencies and percentages of categorical variables, expressed as mean, median, and standard deviation. The chi-square test evaluated the association of oral manifestations according to the presence of comorbidities. Of 89 children, 20.2% had oral manifestations, and mucositis was the most prevalent lesion (12.4%). Of the 18 children with oral manifestations, 12 did not present comorbidities, but 7.9% had multisystem inflammatory syndrome and 5.6% had Kawasaki disease. Results show that children with oral lesions had longer hospital stays. These findings indicate the need for further studies to clarify the relationship between the oral manifestations of COVID-19 in pediatric patients for screening of the virus by dentists.

Keywords: Child; COVID-19; Mouth; Lip; Oral Mucosa.

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Introduction

A new infectious disease outbreak caused by the new Coronavirus (COVID-19) emerged in Wuhan, China, in December 2019, spreading globally months later. This new severe acute respiratory syndrome (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO).[1]

As diagnosis tools were developed, the gold standard test for the virus became the RT-PCR (reverse-transcriptase polymerase chain reaction) performed through the collection of a specimen with a nasal oropharyngeal swab.[2] Although older people are more vulnerable to the virus, individuals of any age can be susceptible to the infection,[3] and children infected with COVID-19 may present no symptoms, given that they have a higher immune response, which can prevent severe damage to vital organs.[4] Importantly, SARS-CoV-2 may be present in the children's gastrointestinal tract, and in the feces, for a longer period than in the respiratory system, thus increasing the chances of transmission.[5]

Children may have milder symptoms and less severe lung inflammation than adults; however, sick children may also develop pneumonia and

chest computed tomography findings reveal ground-glass opacity. Those children often develop fever and gastrointestinal symptoms.[5-7] Rashes are also commonly reported, which may be a secondary cell-mediated immune response after the initial viral infection.[8,9]

Verdoni et al.[10] reported an association of SARS-CoV-2 in children with a severe form of Kawasaki disease, a condition first described by Tomisaku Kawasaki in 1967 as a self-limited acute vasculitis in coronary arteries that affects healthy infants and young children. The prevalence of SARS-CoV-2 in Italy is high, and it varies remarkably in different parts of the world. Among Japanese children, the prevalence is also high.[11] Nevertheless, the cause of the disease still needs clarification.[12] Among the most common signs, the disease can cause conjunctivitis, lip and mouth infection, lymphadenopathy, rash, erythema of the palms and soles, and hardening of the hands and feet.[10] There are reports multisystem inflammatory syndrome in children (MIS-C) cases with an association with previous SARS-CoV-2 infection. MIS-C and Kawasaki disease have the same clinical and laboratory features. It is more prevalent in male Afro-descendants and Hispanics than in the general population.[13]

Several studies also describe comorbidities associated with SARS-CoV-2 in children, such as asthma, Crohn's disease, obesity, and diabetes, as well as oncological comorbidities.[14]

Currently, there are no reports on the oral signs and symptoms of COVID-19 in children in Brazil. Accordingly, this study investigates the oral manifestations of COVID-19 in children hospitalized in Recife, describing the clinical conditions and evaluating whether there is an association with comorbidities. It also verifies if there is an association between the presence of oral lesions and the length of hospital stay and if Kawasaki disease and multisystem inflammatory syndrome are associated with a longer hospital stay.

Methodology

This retrospective study reports on data collected from the health records of children hospitalized at the pediatric ward of the General University Hospital, Recife, Pernambuco, Brazil.

The 12-bed ward is a reference for the hospitalization of children with COVID-19, with the diagnosis confirmed by RT-PCR. The sample included records of 89 children of both sexes, aged 0 to 12 years, hospitalized from March to August 2020 with a confirmed diagnosis of COVID-19.

Data collection comprised the evaluation of pediatric patients' medical records; the presence of oral lesions and general health signs and symptoms such as fever, abdominal pain, vomiting, diarrhea, dyspnea, cough, oxygen saturation less than 95%, runny nose, elevated inflammatory markers, skin rash, and hypotension/shock. Headache, cyanosis, edema of hands and feet, and myalgia were recorded. Comorbidity, length of hospital stay, need for admission to the intensive care unit, need for ventilator support, and changes in chest computed tomography findings were also registered. The presence of comorbidities, Kawasaki disease, multisystem inflammatory syndrome, and length of hospital stay were checked for their association with oral manifestations.

IBM SPSS version 25 was used for the statistical calculations. The data were described as absolute and percentage frequencies for categorical variables using mean, standard deviation, and median. Pearson's chi-square test (significance level of 5%) assessed the association of oral manifestations according to the presence of comorbidities.

This study was conducted in compliance with CNS Resolution 466/2012 and approved by the Research Ethics Committee on Human Beings (process no. 4.346.698 and CAAE: 38041120.6.0000.5195).

Results

The sample included 89 medical records of hospitalized children with a confirmed diagnosis of COVID-19 in the period from March to August 2020. Medical records with incomplete information (n = 15) were excluded.

Table 1 shows that most individuals were aged 2 to 5 years and that 60.7% were male and 39.3% were female. Of the children with comorbidities (42.7%), asthma was the most prevalent condition (10.1%).

The general signs and symptoms presented were fever (69.7%), abdominal pain/vomiting/diarrhea (39.3%), dyspnea (36.0%), cough (34.8%), O2 saturation below 95% (24.7%), runny nose (24.7%), high levels of inflammatory markers (21.3%), skin rash (15.7%), hypotension/shock (15.7%), headache (10.1%), cyanosis (10.1%), hand and foot edema (5.6%), and myalgia (3.4%). As for abnormal chest computed tomography findings, 21.3% presented ground-glass opacity. The length of hospital stay ranged from 4 to 6 days (37.1%) and 31.5% of the children needed ventilator support, whereas 33.7% required admission to the intensive care unit. Multisystem inflammatory syndrome was present in 7.9% and Kawasaki disease in 5.6% of the children (Table 2).

Table 3 shows the prevalence of oral manifestations according to the presence of comorbidities. Six children presented oral manifestations and had comorbidities, and 12 children had no comorbidities and presented oral manifestations. Of the children who did not present oral manifestations, 32 had some comorbidities and 39 had no associated comorbidity, which was not statistically significant (p= 0.432).

Of the 18 children with oral manifestations, 11% were admitted for 1 to 3 days. Of the total number of admissions, 33% of the children stayed in hospital from 4 to 6 days, 28% stayed from 7 to 10 days, and 28% stayed over 10 days (Table 4).

Table 5 shows that all five children who had Kawasaki disease had oral manifestations. Of the seven (100.0%) children who had multisystem inflammatory syndrome, five (71%) had oral manifestations. There was no association between Kawasaki disease and multisystem inflammatory syndrome with oral manifestations (p(1) = 0.470); however, there was a statistically significant association between oral manifestation and length of hospital stay. Children with oral lesions stayed in hospital from 7 to 10 days, p (1) = 0.050) (Table 6).

Discussion

At the beginning of the pandemic, COVID-19 was more prevalent in adults; however, children also presented the infection as it progressed

Table 1. Demographics and comorbidities.

Variable	n (%)
OVERALL	89 (100.0)
Age group	
< 1 year	12 (13.5)
1	16 (18.0)
2–5	23 (25.8)
6–9	22 (24.7)
10–12	16 (18.0)
Sex	
Male	54 (60.7)
Female	35 (39.3)
Presence of comorbidities	38 (42.7)
Asthma	9 (10.1)
Acute lymphoblastic leukemia	3 (3.4)
Wheezing	3 (3.4)
Nephrotic syndrome	2 (2.2)
Congenital Zika syndrome	2 (2.2)
Obesity	2 (2.2)
Down's syndrome	2 (2.2)
Gastroesophageal reflux disease	1 (1.1)
Congenital clubfoot	1 (1.1)
Hypomelanosis of Ito	1 (1.1)
Immunodeficiency	1 (1.1)
Acute megacarioblastic leukemia	1 (1.1)
Bronchospasm	1 (1.1)
Progressing ependymoma	1 (1.1)
Delay in neuropsychomotor development	1 (1.1)
Whooping cough	1 (1.1)
Bone marrow transplant 2 years ago	1 (1.1)
Adrenoleukodystrophy	1 (1.1)
Acute disseminated encephalomyelitis	1 (1.1)
Rectal prolapse	1 (1.1)
Rib fractures	1 (1.1)
Hypertension	1 (1.1)
Cow's milk protein allergy	1 (1.1)
ADNP syndrome	1 (1.1)
Previous acute viral bronchiolitis	1 (1.1)
Malnutrition	1 (1.1)
Swallowing disorders	1 (1.1)
Neuroblastoma IV	1 (1.1)
Sickle cell anemia	1 (1.1)
Epilepsy	1 (1.1)
Prematurity	1 (1.1)
Diabetes mellitus	1 (1.1)
Microcephaly	1 (1.1)
Hydrocephalus with ventriculoperitoneal shunt	1 (1.1)
Bilateral hydronephrosis	1 (1.1)
Cystic fibrosis	1 (1.1)

Table 2. Evaluation of the children's medical records.

Variable	n (%)
Overall	89 (100.0)
Signs and symptoms	
Fever	62 (69.7)
Abdominal pain/vomiting/diarrhea	35 (39.3)
Dyspnea	32 (36.0)
Cough	31 (34.8)
O_2 saturation less than 95%	22 (24.7)
Coryza	22 (24.7)
High levels of inflammatory markers	19 (21.3)
Skin rash	14 (15.7)
Hypotension/shock	14 (15.7)
Headache	9 (10.1)
Cyanosis	9 (10.1)
Edema of hand and feet	5 (5.6)
Myalgia	3 (3.4)
Ventilatory support	
No	61 (68.5)
Yes, catheter	22 (24.7)
Yes, assisted ventilation	6 (6.7)
ICU admission	30 (33.7)
Abnormal chest computed tomography findings	30 (33.7)
Chest CT: ground-glass opacity	19 (21.3)
Another possible diagnosis	12 (13.5)
Diagnosis of multisystem inflammatory syndrome	7 (7.9)
Diagnosis of Kawasaki disease	5 (5.6)
Presence of oral manifestations	18 (20.2)
Oral manifestations:	
None	71 (79.8)
Mucositis	11 (12.4)
Aphthous stomatitis	2 (2.2)
Dentoalveolar abscess	1 (1.1)
Hyperemic lips	1 (1.1)
Exfoliative cheilitis	1 (1.1)
Impetigo	1 (1.1)
Gingivitis	1 (1.1)
Length of hospital stay (days)	
1–3	26 (29.2)
4–6	33 (37.1)
7–10	12 (13.5)
More than 10	18 (20.2)

across continents. This study indicates that the severity of the infection proved to be associated with the presence of oral lesions, as reported by Lai et al.[15]

The data obtained from the medical records corroborate the findings of Moraes et al.,[16] indicating that the children's health conditions may develop into severe respiratory implications. There are reports that children with comorbidities are more prone to be infected by SARS-CoV-2. However, the most prevalent comorbidity found in this study was asthma, which worsens the respiratory condition, triggering immune responses of lung cells.

Interestingly enough, studies by Sousa et al.[17] indicated the viruses could affect the gingival tissue, causing airway inflammation in patients with asthma. Therefore, the dentist and the multidisciplinary team should apply methods to optimize dental biofilm control in compromised children, a simple action that may prevent deterioration of the respiratory condition.

In this study, most patients presented with fever – the same findings reported by Cai et al.[18] and Castagnoli et al.[19] Pediatric dentists are aware that fever indicates infections, and by taking into account that there is a global pandemic and that current protocols recommend chest CT scans, a trained dental practitioner may be able to prescribe a chest image exam to identify ground-glass opacity in the lungs, the main feature of COVID-19.[20] Although most pediatric patients are asymptomatic, SARS-CoV-2 may enter airway cells through angiotensin 2 converting enzyme (ACE2) receptors, triggering the massive release of inflammatory cytokines and causing tissue necrosis. Nevertheless, it is not yet clear whether the maturity, functionality, or affinity of ACE2 receptors are lower in children than in adults, as reported by Song et al.[21] Some other children develop severe diseases, requiring hospitalization and intensive care treatment.[22]

According to the assessed medical records, some children had multisystem inflammatory syndrome, also described in reports by Jones et al.[23] MIS-C is a severe condition that requires hospital facilities for treatment because of the intense inflammatory reaction with persistent fever, leading to shock and

Table 3. Prevalence of oral manifestations according to comorbidities.

Comorbidities	Oral manifestations n (%)		Overall n (%)	p-value	OR (95%CI)
	Yes	No			
Yes	6 (15.8)	32 (84.2)	38 (100.0)	0.432*	1.0
No	12 (23.5)	39 (76.5)	51 (100.0)		1.6 (0.6 –4.9)
Total group	18 (20.2)	71 (79.8)	89 (100.0)		

*Fisher's exact test.

Table 4. Oral manifestations according to the length of hospital stay.

Variable	n (%)
Occurrence of oral manifestations according of hospital stay (days)	18 (100.0)
1–3	2 (11)
4–6	6 (33)
7–10	5 (28)
More than 10	5 (28)

Table 5. Oral manifestations according to Kawasaki disease and Multisystem Inflammatory syndrome.

Diagnosis	Oral manifestations n (%)		Overall n (%)	p-value
	Yes	No		
Kawasaki disease	5 (100.0)	0 (0)	5 (100.0)	0.470*
Multisystem Inflammatory syndrome	5 (71.4)	2 (28.6)	7 (100.0)	
Total group	10 (83.2)	71 (79.8)	89 (100.0)	

*Fisher´s Exact test.

Table 6. Oral manifestations according to the length of hospital admission.

Oral manifestations	1–3	4–6	7–10	More than 10	Overall	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Absence of oral manifestations	24 (92,3)	27 (81,8)	7 (58,3)	13 (72,2)	71 (79,8)	0.050*
Mucositis	0 (0,0)	3 (9,1)	4 (33,3)	4 (22,2)	11 (12,4)	
Others	4 (7,7)	3 (9,1)	1 (8,3)	1 (5,6)	7 (7,9)	
Total group	28 (100.0)	33 (100.0)	12 (100.0)	18 (100.0)	89 (100.0)	

*Fisher´s Exact test.

multiple organ failure. Still, there is no scientific evidence of the association of the clinical features of SARS-CoV-2 infection with MIS-C, but reports have indicated that the most affected children had contact with the COVID-19 virus.[24]

Currently, not much evidence is available about MIS-C; therefore, its epidemiological features, signs, and symptoms should still be a target of further studies. Thus, at present, several case reports and case series have described a severe multisystem inflammatory syndrome with the same clinical and laboratory characteristics as Kawasaki disease, staphylococcal or streptococcal toxic shock syndrome, bacterial sepsis, and macrophage activation syndrome.[25,26]

According to data from the European Center for Disease Prevention and Control[27] and The Royal College of Pediatrics and Child Health,[28] children older than five years have higher chances

of developing heart conditions, more prevalent among Afro-descendants. Note that the Brazilian population treated at public hospitals under the National Health System are primarily blacks or Afro-descendants. Furthermore, some children in this study were diagnosed with Kawasaki disease which, according to the Brazilian Society of Pediatrics[29] and Sundel et al.,[30] may lead to high temperature for at least five days, associated with at least four of the five other signs established by the American Heart Association (AHA). They may also have lip and mouth lesions, conjunctival hyperemia, changes in extremities, skin rash, and cervical lymphadenopathy. Lip and oral lesions include erythema, dryness, fissures, and lip bleeding, as also reported by Halboub et al.[31]

Oral lesions may be a sign of more severe oral infection, and mucositis was the most commonly found condition in this sample, described as an inflammatory or ulcerated lesion. It is important to emphasize that 56% of the children who presented oral manifestations had hospital stay equal to or greater than seven days. These findings are in line with those of the study by Beatrice et al.,[32] who reported hospital stay for over one week among children. Thus, although children aged less than five years required much less hospitalization and intensive care, some of the children in this report remained hospitalized for more than 10 days.

This study did not find a significant association between children who had Kawasaki disease and multisystem inflammatory syndrome with the presence of oral lesions. A systematic review by Yasuhara et al.[33] described symptoms overlapping with Kawasaki disease, such as oral erythema and swelling of the tongue, lips, and lingual papillae. It is therefore clear that dentists can help with the detection of viruses, preventing them from spreading and infecting older people.[34]

Iranmanesh et al.[35] reported a relationship between the severity of the disease, comorbidities, and oral lesions, unlike the present study, which did not find any significant association between the presence of comorbidities and the presence of oral manifestations. This study pointed out that the severity of the disease, with the development of oral lesions, kept children in hospital for longer periods.

This study presents limitations regarding the reliability of the data collection, including assessment bias. The authors suggest that more studies could provide pediatric dentists with more knowledge about the oral signs of SARS-CoV-2 and the management of sick children.

Conclusion

This study reveals that children with SARS-CoV-2 with oral lesions stay longer in hospital and have more severe conditions.

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