The appearance of oral manifestations in children infected with COVID-19: A critical review of the literature.

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Abstract

Objective:
The aim of this narrative review of the literature is to summarize the evidence on the prevalence of oral manifestations and to ascertain at what point in time oral manifestations present in children infected with SARS-CoV-2.

Method:
Databases PUBMED, Google Scholar and Ebsco were used. The search terms: COVID 19, oral manifestations and child, along with age filters were applied to generate the articles published between 2020-2021.The abstracts of the articles were first read and then those articles that were relevant were evaluated in detail.

Results:
Hyperaemic pharynx and dysgeusia were prevalent in children with COVID-19 disease while edematous and erythematous lips and strawberry tongue were frequently seen in patients diagnosed with multisystem inflammatory syndrome in children. In some sources the onset of oral manifestations was unclear resulting in inconclusive evidence.

Conclusion:
Oral manifestations are commonly seen amongst the earliest manifestations of COVID-19, and may happen prior to presenting other symptoms, or up to a week after other manifestations of the disease. The appearance of oral manifestations in children with COVID -19 like symptoms may be an indicator of disease severity and the likelihood that disease progression could potentially be more severe and have more detrimental outcomes.

BACKGROUND

The novel coronavirus disease (COVID-19) is less prevalent in children than in adults.[1] The lower prevalence in this population has been attributed to the lessened expression of angiotensin-converting enzyme-2 (ACE 2)[2,3], and the presence of different viruses that possibly compete with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. In addition to low infectivity in children and adolescents, this population experiences less severe symptoms, shorter course of disease and a good prognosis, when compared to adults[4]. It should be noted that this lower prevalence could be underestimated due to the common asymptomatic nature of the disease in children which could lead to less testing in this population.[1]

Multisystem inflammatory syndrome in children (MIS-C) is defined as presenting a high fever, evidence of C-reactive protein ≥3.0 mg/dL (30 mg/L), new onset manifestation in at least two of the following: cardiac, mucotaneous, shock, gastrointestinal and haematologic involvement, in addition to the detection of SARS-CoV-2.[5]There are notable similarities between MIS-C and Kawasaki disease, in which patients present systemic vasculitis.[6] Findings from a retrospective review study of 47 pediatric patients, conducted in a hospital setting have suggested that oral and oropharyngeal manifestations with COVID-19, could potentially be early indicators of (MIS-C) and were significantly associated with other diagnostic symptoms of MIS-C such as systemic rash and conjunctivitis[7], however little is known about how soon the oral manifestations present in children. Therefore, the aim of this narrative review was firstly to summarize the oral manifestations seen in children and secondarily to ascertain when oral manifestations present in children infected with SARS-CoV-2.

METHODOLOGY

For this narrative review of the literature, articles were retrieved from PubMed using the MESH terms COVID-19, COVID 19, oral manifestations and the filters: free full text, adolescents: 13-18, child: birth -18 years, child: 6-12 years were applied. The abstracts were all read and those articles which were relevant to the aim of this review were read in detail. The references of the selected articles were checked to find more relevant articles. Google Scholar and EBSCO were also checked for relevant articles using the search terms COVID 19, oral manifestations and child. Where articles were not freely available, the authors were contacted, and requests were made. Only articles in the English language were included in this review and were published between the years 2020 and 2021. The types of articles included were case reports, case series, cross-sectional, cohort and review studies.

RESULTS

The literature search identified 19 relevant articles. Table 1 shows the summary of the prevalence findings in children with COVID-19 and those diagnosed with MIS-C.

Prevalence of oral manifestations in children with COVID-19 disease

In a retrospective study including 27 children aged between 3 months to 14 years old, the following oral manifestations were noted: oral pseudomembranous candidiasis (7.4%, n=2), geographic tongue (3.7%, n=1), coated tongue (7.4%, n=2), hyperaemic pharynx (37%, n=10) and taste alteration (11.1%, n=3).[8]

Prevalence of oral manifestations in patients diagnosed with MIS-C

A retrospective study, showed that edematous and erythematous lips (48.9%, n=23) and strawberry tongue (10.6%, n=5) were seen in 47 children who were diagnosed with MIS-C. Other oral manifestations seen in this population that were considered to be less prevalent were sores, mouth pain, oropharyngeal erythema, smile asymmetry and tongue deviation.[7]

In a systematic review that included 662 children with MIS-C, it was found that 4.7%(n=31) had tongue swelling and 51%(n=343) presented with cheilitis.[9]

Amongst 84 patients with MIS-C, red, swollen lips (27.3%) and other unspecified changes in the mouth (19%) were reported in a systematic review.[10]

Changes in the oral mucosa, dry and red lips were classified as unspecified oral manifestations (n=185) in a review study were seen in 25-87% of the children with MIS-C.[11]

Table 1. Summary of prevalence findings of oral manifestations in children with COVID-19 disease.

Study	Study design	Data collection period	Sample size	Age	Oral manifestation	MIS-C diagnosis
Bardellini et al. 2021[8]	Retrospective cross-sectional study	March-April 2020	27	Mean 4.2 ±1.7	oral pseudomembranous candidiasis n=2 (7.4 %) geographic tongue n= 1 (3.7%) coated tongue n=2 (7.4%) hyperaemic pharynx n=10 (37 %), dysgeusia n=3 (11%)	No
Halepas et al. 2021[7]	Retrospective cross-sectional study	March-June 2020	47	Mean 9 ± 5	Red, cracked lips n= 23 (48.9%) Strawberry tongue n = 5 (10.6%) Other oral manifestations n=7 (14.9%)	Yes
Ahmed et al. 2020 [9]	Systematic review	January – July 2020	662	Mean 9.3 ± 0.5	Cheilitis n = 216 (32.6%) Tongue Swelling n = 31 (4.7%)	Yes
Bhujel et al. 2021[10]	Systematic review	March 2020	84	Range 3 months-20 years	Oral pseudomembranous candidiasis n = 2 (2%) Geographic tongue n = 1 (1%) Coated tongue n = 2 (2%) Red or swollen lips n =23 (27%) Strawberry tongue n=5 (6.0%) Oral cavity changes unspecified n=16 (19.0%)	Yes
Naka et al. 2021[11]	Literature review	January 2021	452	Median 8-12	Dry and red lips and/or other mucosal changes in 25%–87% of 185 cases of oral manifestations.	Yes
Whittaker et al. 2020[12]	Cross-sectional study	March-May 2020	58	Median 9 years old	Mucous membrane changes and red cracked lips n = 11, (25%)	Yes
Rekhtman et al. 2020 [13]	Cohort study	May 2020	31	Range 1.75-16 years old	MIS-C group: Lip fissuring n=4 (21%), tongue papillitis n=2 (11%) COVID-19 group: Lip fissuring n=1 (8%)	Yes

A case series including 58 children with MIS-C also reported mucous membrane changes and red, cracked lips in 25% (n=11).[12]

One cohort study compared MIS-C (n=19) and children diagnosed with COVID-19, and found that in the MIS-C group, 21% (n=4) presented fissured lips and 11% (n=2) presented tongue papillitis while the COVID-19 group presented 8% (n=1) fissured lips.[13]

Zaheer et. al 2022 [14], affirms that the oral lesions seen in the studies [9,10, 11,12,13] involved the lips and tongue. The most frequently reported symptoms in these cases were cheilitis, tongue swelling and dry and red mucosal membranes.

Length of time from onset of COVID-19 to the appearance of oral manifestations.

Table 2 shows summary of studies of the timing of oral manifestations relative to other symptoms in children with COVID-19 disease. Oral manifestations such as vesicles and erosions on the anterior tongue, lips and buccal mucosa were noted in a 9-year-old female who tested positive for SARS-COV-2.[15,16] These oral manifestations preceded by 3 days other common symptoms associated with COVID-19 such as dry cough, somnolence, tachypnea and hypoxia.

A 15-year-old male, presented with dysgeusia described as a transient metallic taste when eating that improved after 12 days.[2] Of note, this oral manifestation began 3 days prior to the manifestation of ear, nose, and throat (ENT) symptoms (sore throat, runny nose and nasal congestion) as such was considered as a sentinel symptom.[2]

Three SARS -CoV-2 positive neonates (2 males and a female) admitted to the hospital, oral candidiasis was found to be present in each neonate. Two of the neonates were asymptomatic and only one experienced COVID-19 related symptoms such as coughing, lethargy and fever. It was unclear at what point the oral candidiasis developed in each child. The relationship between antibiotics and oral candidiasis is well known, however this was ruled out as the possible cause, as only the symptomatic neonate was administered antibiotics, and this was after the patient presented the oral candidiasis.[17]

In a retrospective study in which the mean age of COVID-19 infected patients was 4 years old (4,2 $\pm$ 1,7), it was self-reported that geographic tongue appeared concomitantly with elevated fever.[8]

A two- year-old female infected with COVID-19, developed a localized gingival inflammation between the right maxillary incisor and canine the same day she experienced other symptoms such as a fever, nausea, and vomiting. A week later several white lesions appeared on the labial mucosa along with desquamation of the epithelium and was otherwise asymptomatic.[18]

A 6 -year -old male who was initially asymptomatic, notwithstanding loss of appetite and transient anosmia 2 weeks prior to hospitalization, presented with severe erythema multiforme which included, substantial labial crusting, gingival erosions, and a target lesion on the face. The lesions developed a week before hospitalization and no respiratory symptoms were observed in this patient.[19]

A 12- year- old female presented with facial exanthema and a coated swollen tongue with pronounced papillae (strawberry tongue) when her fever had subdued after three days. The only other symptoms reported were fatigue and headache.[20] Three weeks after having a 5 day fever, along with coughing and prolonged diarrhea, a 9-year-old male developed symptomatic glossitis, along with other dermatologic symptoms and conjunctivitis.[21] Of note, this patient had Down's syndrome and alopecia areata universalis [21] unlike all the previous cases in which the children did not have any underlying illnesses prior to contracting COVID-19. The oral manifestation may therefore be atypical when compared to other children.

Length of time from onset of COVID-19 to the appearance of oral manifestations in patients diagnosed with MIS-C or Kawasaki disease.

A 6-month-old diagnosed with Kawasaki disease associated with COVID-19, presented with dry cracked lips (after 2 days of fever) and prominent tongue papilla (after 5 days of fever).[22.]

Fissured lips were observed in a 12-year-old male with a history of 6 days of fever along with other symptoms such as respiratory and gastrointestinal distress. Similarly, fissured lips was observed in a 5 year old female patient with a four day history of fever along with gastrointestinal symptoms, nuchal rigidity and swollen hands.[23] Another 9-year-old female patient developed fissured lips and strawberry tongue on the fifth day of hospitalization. Prior to her hospitalization, she presented with fever, and gastrointestinal distress.[23] It is important to note that all three cases were diagnosed as MIS-C.

Table 2. Summary of studies showing the timing of oral manifestations relative to other symptoms in children with COVID-19 or MIS-C disease.

Study	Country of origin	Study design	No. of cases	Age	Sex	Oral manifestation	Location of oral manifestation	Length of time from onset of illness to appearance of oral manifestations	Systemic disease
Aghzadeh et al. 2020 [15]	Iran	Case report	1	09 years	F	Vesicles and erosions	Lips, tongue, buccal mucosa1	3 days prior to respiratory symptoms	none
Maniaci et al. 2020 [2]	Italy	Case report	1	15years	M	Dysgeusia		3 days prior to ENT symptoms	none
Dima et al. 2020[17]	Romania	Case report	3	neonate	M	Oral candidiasis	n/a	unclear	none
				neonate	M		n/a	unclear	none
				neonate	F		n/a	unclear	none
Bardellini et al. 2021 [8]	Italy	Retrospective study	27	n/a	n/a	Geographic Tongue		Concurrently with high fever	none
Neskovich et al. 2021[18]	Serbia	Case report	1	2 years	F	Gingival Inflammation	Between the upper right maxillary incisor and canine region	Concurrently	none
						Diffuse white lesions	Labial mucosa	1 week after	none
Labe et al. 2020[19]	France	Case report	2	6 years	M	Erythema multiforme	Lips	1 week after	none
				3 years	M	Glossitis	Tongue	unclear	Kawasaki disease

Olisova et al. 2020 [20]	Russia	Case report	1	12 years	F	Strawberry tongue, glossitis	Tongue	3 days after	none
Mazzotta et al. 2020 [21]	Italy	Case report	1	9 years	M	Glossitis	Tongue	3 weeks after	Down's syndrome Alopecia areata universalis
Jones et al. 2020 [22]	United States of America	Case report	1	6 months	F	Fissured lips Strawberry tongue	Lips Tongue	2 days after 5 days after	Kawasaki disease
Chiotos et al. 2020 [23]	United States of America	Case series	3	12 years	M	Fissured lips	Lips	6 days after	MIS-C
				5 years	F	Fissured lips		4 days after	MIS-C
				9 years	F	Fissured lips Strawberry tongue	Tongue	5 days after	MIS-C
Chiu et al. 2020 [24]	United States of America	Case report	1	10 years	M	Fissured lips Erythema	Lips oropharynx	7 days after	Kawasaki disease

F-female, M-male

In another case of a 10- year- old, male patient diagnosed with COVID-19 associated Kawasaki disease, a mildly erythematous oropharynx and slight fissured lips were observed after a 7-day period of fever. The patient also had a cough, rash, diarrhea, and conjunctivitis.[24]

Similarly, a 3-year-old male who was admitted for having 8 days of fever, also showed no respiratory symptoms, but presented with glossitis, conjunctivitis, pulmonary involvement, and other manifestations of the skin and was therefore diagnosed with Kawasaki disease.[19]

DISCUSSION

This literature review is a compilation of different cases in which oral manifestations were observed in children diagnosed with COVID-19. Though the different reports included children of different ages and sex, it is unclear whether either play a role in the appearance of oral manifestations. Further studies should be carried out to investigate the potential role of age and sex as indicators for oral and other manifestations of COVID-19.

The most prevalent oral manifestations seen in children diagnosed with COVID-19 disease were

hyperaemic pharynx and dysgeusia [8]. Viral pharyngitis can result in this hyperaemic aspect of the pharynx which is consistent with an upper respiratory tract infection.[8] Dysgeusia is thought to occur due to the presence of ACE 2 receptors for SARS-CoV-2 on the oral and nasal mucosa.[25]

On the other hand, children diagnosed with MIS-C the most common findings were changes in the labial mucosa[7,10,11,12,13], cheilitis[9] and strawberry tongue.[10,13] Furthermore, oral mucosa changes were found to be the second most prevalent clinical findings (58%) in a metanalysis that included 318 COVID-19 pediatric patients diagnosed with MIS-C.[26]

It is possible that given the severity of other symptoms in children with MIS-C that changes in the oral cavity go unperceived and so the incidence of oral manifestations may be undetected and thus underreported.[7] It was noted that some of the oral manifestations seen in individuals with MIS-C were recorded as unspecified lesions, possibly due to the inability of medical physicians to correctly classify oral lesions. This potentially affects the true estimation of the prevalence of specific oral manifestations in persons with MIS-C. This is also coupled by perhaps the inability of small children to self-report symptoms, possibly leading to a lower prevalence of oral manifestations reported in the literature.[8]

It is likely that there are no particular oral manifestations associated with children infected with SARS-COV-2 but rather, oral lesions that may be seen in other common viral infections as well.[8] Similarly to SARS-COV-2, many viruses may present different or the same clinical manifestations based on viral load, the type of variant, organotropism, host reaction and age.[21, 27.]

Fever is the main symptom seen in children [4,28,29,30], this corroborates with the reported cases in which most children had a fever before later developing oral manifestations and other symptoms. In fact, in addition to fever and fatigue, oral and skin lesions may be the only clinical signs and symptoms of COVID-19 in children perhaps due to the increase in T cells which conveys some immunity against viruses.[20,31.]

CONCLUSION

Prevalent oral manifestations seen in children with COVID-19 were hyperaemic pharynx and dysgeusia. Common oral manifestations seen in those diagnosed with MIS-C were fissured lips, cheilitis and strawberry tongue. Based on a wide variation of symptoms and time of appearance, it cannot be concluded that the presence of oral manifestations could definitively be considered as a sentinel symptom. However, given the common belief that symptoms in children are usually less severe, the appearance of oral manifestations, in a child with COVID -19 like symptoms may be considered as a warning sign that the disease could potentially be more severe and have more serious outcomes, as in the case of MIS-C. Oral manifestations may be seen amongst the earliest manifestations of acute COVID-19 in children, and may happen prior to presenting other symptoms. In the case of MIS-C, oral manifestations may occur up to a week after other manifestations of the disease. Dentists should be trained in recognizing the oral manifestations associated with SARS-COV-2 that could aid in the early diagnosis of COVID-19 in children or the potentially fatal MIS-C if left undiagnosed.

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