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Association among COVID-19, multisystem inflammatory syndrome in children, and oral health status

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Abstract: The pathophysiology of multisystem inflammatory syndrome in children (MIS-C) and associated oral symptoms have not been clarified yet. The aim of the present study was to compare the oral health status of children with MIS-C-associated Coronavirus disease 2019 (COVID-19) and COVID-19. A total of 54 children with SARS-CoV-2 infection, 23 with MIS-C-associated COVID-19 and 31 with asymptomatic, mild, and moderate COVID-19 were recruited for the present cross-sectional study. Sociodemographic variables, medical examinations, oral hygiene habits, and extraoral and intraoral findings (DMFT/dmft index, OHI scores, and oral mucosal changes) were recorded. The t-test for independent samples and the Mann-Whitney U test were used ($p < 0.05$). MIS-C was found to be associated with chapped lips (all patients) and oral mucosal changes, including erythema, white lesion, strawberry tongue, and swelling of the gingiva as compared to the COVID-19 group (frequency of more than one mucosal change: 100% vs. 35%) ($p < 0.001$). Children with MIS-C presented higher DMFT/dmft scores (DMFT/dmft 5.52 ± 3.16 for the MIS-C group vs. 2.26 ± 1.80 for the COVID-19 group) ($p < 0.01$). Elevated OHI scores were also associated with MIS-C (mean ± SD: 3.06 ± 1.02 (MIS-C) vs. 2.41 ± 0.97 (COVID-19) ($p < 0.05$). Oral manifestations, mainly strawberry and erythematous tongue, were characteristic features of MIS-C. Prevalence of oral/dental symptoms was elevated in children with MIS-C when compared to COVID-19. Therefore, dental professionals should be aware of the oral manifestations associated with MIS-C, which may have high mortality and morbidity rates.

Keywords: Child; COVID-19; Multisystem Inflammatory Syndrome in Children (MIS-C); Oral Health.

Introduction

It has been reported that the clinical course of COVID-19 due to SARS-CoV-2 infection in children is mild, and its incidence is low (2%) compared to adults and older people.[1,2] When the severity of the cases was evaluated, 90% of them were asymptomatic, had a mild or moderate course, recovered within 1–2 weeks, and had a good prognosis; so the risk of severe disease was low.[1-3]

In April 2020, a disease similar to incomplete Kawasaki disease or toxic shock syndrome was detected in the United Kingdom. This condition, detected post-COVID-19, was termed as multisystem inflammatory syndrome in children (MIS-C). In addition, the disease is also called pediatric multisystem inflammatory syndrome, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock.[3-12] The main clinical symptoms are persistent fever, gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea), rash, and conjunctivitis.[1-4] Patients typically present to the clinic after developing shock and/or multisystem involvement following a fever for 3–5 days.[4] The pathophysiology of MIS-C is not fully understood yet; it is thought to occur as a result of an abnormal immune response to the virus or related to immune dysregulation.[13]

In addition, oral symptoms are observed in children with COVID-19 and MIS-C, and it is stated that these symptoms might play an important role in diagnosis and patient management.[1,6,8] However, the exact pathophysiology of oral manifestations of SARS-CoV-2 infection and MIS-C is currently unknown.[6] In COVID-19, the role of the abundance of angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease serine 2 expressed in the respiratory tract and in the oral mucosa, including the tongue, gingiva, and salivary glands, has been hypothesized as a responsible pathway. These cell receptors within the oral cavity have been shown to aid the entry of the virus into the host.[6,13] Also, ACE-2 receptors on tongue biofilm may play an important role in the entry of SARS-CoV-2 into host cells, and patients with high ACE-2 expression may be more susceptible to SARS-CoV-2 infection.[9]

Oral mucosal irritation, strawberry tongue, redness, and swelling of the tongue and lips can be seen in the oral findings of children with COVID-19 and MIS-C.[5-7,10,14,15]Studies have shown that adult patients with poor oral hygiene (increased dental plaque scores and number of dental caries) had more severe COVID-19 complications.[16-18] It has been shown that cariogenic bacteria in the oral biofilm may affect the severity of COVID-19 complications, given that the oral cavity is responsible for the development of hospital-acquired pneumonia and creates a reservoir for respiratory pathogens.[9,19-23]

It has been emphasized that oral hygiene is important in terms of the course of the disease in children who had COVID-19 and MIS-C, as observed in adults. Therefore, the present study aimed to compare the oral health status of children with SARS-CoV-2 virus infection and MIS-C associated with COVID-19.

Methodology

Inclusion and exclusion criteria

Children aged 5 to 15 years who had COVID-19 and MIS-C and were treated between November 2021 and February 2022 at the Division of Pediatric Infectious Diseases of the Children's Hospital affiliated with the Dokuz Eylul University, were included. In order to eliminate the problems that may occur in dentition due to preterm birth, the birth week of all patients was provided by their parents, and preterm babies were excluded from the study. Children with severe COVID-19 were excluded from the study as well. The study protocol was approved by the Research Ethics Committee of the Dokuz Eylul University (2022/01–22). The study followed the STROBE guidelines for observational studies.

The children's oral findings were evaluated through a questionnaire, including demographic characteristics and oral hygiene habits of the patients and their parents. An assent form and an informed consent form were signed by the children and their parents, respectively.

Medical examinations

MIS-C was diagnosed according to the MIS-C diagnostic criteria established by the Centers for Disease Control and Prevention (CDC) and WHO.[24,25] A confirmed case of COVID-19 was defined as a positive RT-PCR result for a nasopharyngeal swab specimen.

Asymptomatic COVID-19 disease is defined as asymptomatic cases with positive PCR. Cases with symptoms of upper respiratory tract infection were defined as mild disease; cases with lower respiratory

tract infection and no oxygen requirement were defined as moderate disease; and cases with lower respiratory tract infection and oxygen need were defined as severe disease. Cases requiring non-invasive/invasive mechanical ventilation and sepsis or multi-organ failure were considered as critical diseases.[26] Children with asymptomatic, mild, or moderate disease were included in the study. Intraoral lesions in children diagnosed with COVID-19 and MIS-C were evaluated at the Pediatric Infectious Diseases Clinic.

Intraoral findings (strawberry tongue, chapped lips, whiteness on the tongue surface, and rusty appearance on the tongue) observed when the children had COVID-19 and MIS-C were recorded clinically. Following the treatment and the recovery period (2-4 weeks thereafter), the patients were recalled to the Division of Pediatric Infectious Diseases for a routine check-up. Demographic characteristics and clinical data were retrieved from the patient records.

Oral and dental examinations

The present study was conducted at one of the largest university hospitals in the region. Cases were referred from other regional hospitals and different towns or cities when they were difficult or inadequate to treat. The increase in MIS-C cases correlated with the COVID-19 pandemic led us to conduct the present study.

During the oral examination of the patients diagnosed with COVID-19 and MIS-C seen at the University's Pediatric Infectious Diseases Clinic for routine control (with a mouth mirror and a probe in the clinical setting), DMFT (decayed missing or filled teeth) index for permanent teeth, dmft index[16] for deciduous teeth, and oral hygiene index[17] were recorded.

Briefly, the DMFT index, a method for measuring present (decayed teeth) and past (missing and filled teeth) caries experiences in the primary and permanent dentitions, was evaluated.[16] The oral hygiene index (OHI) shows the patient's oral hygiene status and indicates the presence of plaque on the surface of the teeth. OHI allows for determining the presence of dental plaque and calculus. This method allows investigating and determining the numerical presence of soft plaque, classified into four classes from 0 to 3.[17] The qualitative criteria of this index range from 0 to 6 when the sum of debris and calculus can be classified as: excellent (0.0), good (0.1–1.2), regular (1.3–3.0), and weak (3.1–6.0). When only the bacterial plaque was counted, the classification was as follows: good (0.0 to 0.6), regular (0.7 to 1.8), and poor (1.9 to 3.0).

The children's oral hygiene habits were evaluated by the following questions: how many times a day do your children brush their teeth?; do they use toothpaste when brushing their teeth?; do you prefer fluoridated toothpaste?; and when did you start brushing your child's teeth?. The evaluation also considered toothbrush replacement period, frequency of regular dental check-ups (at least once a year), and whether there was bleeding during toothbrushing (Table 1).

Neither radiographic examination nor dental treatment was performed on any of the children. DMFT and/or dmft and OHI evaluation were performed by an experienced pediatric dentist (G.K.) and a periodontist (B.C.U.).

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences version 22 (IBM Corp., Armonk, USA). Descriptive statistics of the numerical variables were calculated as mean±standard deviation, and categorical variables were expressed as a percentage (%). The chi-square test was used to compare the categorical variables between the groups, and the t-test for independent samples was used to compare the numerical variables between the groups if the assumptions were met; otherwise, the Mann-Whitney U test was used. A p-value of 0.05 was set as significant.

Results

Clinical characteristics of the patients

Twenty-three (42.6%) children were diagnosed with MIS-C associated with COVID-19 and were hospitalized. Thirty-one (57.4%) children who had COVID-19 were evaluated at the Dokuz Eylul

Table 1. Oral hygiene habits

Oral hygiene habits	MIS – C	COVID-19	p-value
	n = 23 (%)	n = 31 (%)	
Toothbrushing frequency (daily)			
Occasionally	14 (60.9)	16 (51.6)	0.689
At least once	9 (39.1)	15 (48.4)	
Toothpaste usage			
Yes	22 (95.7)	28 (90.3)	N/A
No	1 (4.3)	3 (9.7)	
Type of toothpaste			
With fluoride	3 (13.0)	4 (12.9)	
Without fluoride	5 (21.7)	2 (6.5)	N/A
Does not know	15 (65.3)	25 (80.6)	
Time to start toothbrushing			
Pre-school	11 (47.8)	18 (58.1)	0.638
School	12 (52.2)	13 (41.9)	
Toothbrush replacement frequency			
Three months	10 (43.5)	13 (41.9)	1.000
More than three months	13 (56.5)	18 (58.1)	
Frequency of dental visits (1 and/or 2 times a year)			
No	7 (30.4)	5 (16.1)	0.358
Visited	16 (69.5)	26 (83.9)	
Bleeding while toothbrushing			
Yes	8 (34.8)	17 (54.8)	0.236
No	15 (65.2)	14 (45.2)	

University's Children's Hospital, Division of Pediatric Infectious Diseases. Age, gender, and educational status of the parents was similar among children with MIS-C and COVID-19 ($p > 0.05$) (Table 2). The mean age of patients with MIS-C was 8.48 ± 3.47, while the mean age of patients with COVID-19 was 10.23 ± 3.07.

Oral hygiene habits

Despite the toothbrushing habits of children with COVID-19 (51.6%), the age at which they start brushing their teeth (58.1%), and the frequency of dental visits once and/or twice a year (83.9%) were higher than among children with MIS-C, the difference was not reached a significance level ($p > 0.05$).

Oral findings

Changes in the lips, gingiva, tongue, and oral mucosa of the children during COVID-19 and MIS-C were evaluated from patient records (Table 3). In our study, one or more oral mucosal changes were detected in all children (100%) during MIS-C disease, while it was observed in 35.5% of those who had COVID-19, and the difference was statistically significant ($p < 0.001$). No difference was detected between the presence of oral lesions among children with MIS-C and COVID-19. All children had chapped lips during the course of MIS-C, which was seen in 25.8% of those with COVID-19. Strawberry tongue (39.1%) and erythematous tongue (30.4%) were observed in

Table 2. Patient demographics.

Demographics	MIS – C	COVID-19	p-value
	n = 23 (%)	n = 31 (%)	
Gender			
Female	7 (30.4)	16 (51.6)	0.201
Male	16 (69.6)	15 (48.4)	
Age (5–15 years)	8.48 ± 3.47	10.23 ± 3.07	0.056
Maternal education			
Primary School–High School	14 (60.9)	19 (61.3)	1.000
University or higher education	9 (39.1)	12 (38.7)	
Paternal education			
Primary School–High School	15 (65.2)	22 (71.0)	0.878
University or higher education	8 (34.8)	9 (29.0)	

Table 3. Extraoral and intraoral findings, DMFT/dmft index, and OHI values

Variables	MIS – C	COVID-19	p-value
	n = 23 (%)	n = 31 (%)	
Findings on lips, gingiva, tongue, and oral mucosa			
Chapped lip	23 (100)	8 (25.8)	0.000*
Strawberry tongue	9 (39.1)	-	
Erythematous tongue	7 (30.4)	-	
White lesion on the tongue surface	3 (13.0)	1 (3.2)	
Swelling of the gingiva and/or palate	3 (13.0)	2 (6.4)	
No finding	-	20 (64.5)	
DMFT/dmft index			
Mean ± SD	5.52 ± 3.16	2.26 ± 1.80	0.001*
No caries, filled and missing	-	6 (19.4)	
Between 1–2	6 (26.1)	13 (41.9)	
Between 3–5	5 (21.7)	10 (32.3)	
More than 6	12 (52.2)	2 (6.4)	
OHI values			
Mean ± SD	3.06 ± 1.02	2.41 ± 0.97	0.022*
Good (0.0–0.6)	-	12.9%	
Regular (0.7–1.8)	56.5%	64.5%	
Poor (1.9–3.0).	43.5%	22.6%	

*$p < 0.05$.

children with MIS-C, but they were not observed in the COVID-19 group. A white lesion on the tongue surface and swelling of the gingiva and/or palate were observed in children with both MIS-C and COVID-19, while a higher rate was observed among children with MIS-C.

The mean DMFT/dmft index was 5.52±3.16 in patients with MIS-C and 2.26±1.80 in the COVID-19 group (p=0.001). While the number of patients with a DMFT/dmft index of 6 and above was 12 (52.2%) in MIS-C, it was 2 (6.4%) in the COVID-19 group. The OHI was 3.06±1.02 in MIS-C patients and 2.41±0.97 in patients with COVID-19, and the difference was statistically significant ($p < 0.022$). While no patients with an OHI of 0.0–1.2 were found in the MIS-C group, the percentage of patients was 56.5% for an OHI of 1.3-3.0 and 43.5% for an OHI of 3.1–6.0, and these rates were found to be 12.9%, 64.5%, and 22.6% in the COVID-19 group, respectively (Table 3).

Discussion

A healthy oral status is closely related to systemic health and plays an important role in preventing many viral and bacterial diseases.[27] The existence of an oral and oropharyngeal relationship between MIS-C and COVID-19 has already been reported.[6,9,10,12] Therefore, the possible association between oral and dental symptoms reported in patients with COVID-19 has been investigated. Briefly, oral and dental lesions were found to be frequent in the investigated patient population with MIS-C and COVID-19, with a higher rate in the MIS-C group.

Although the etiology of oral lesions in COVID-19 is still unknown, several hypotheses were tested such as SARS-Cov-2 infection as a primary focus and effect of COVID-19 treatment regimens and stress.[6,7] Therefore, it is likely that oral or oropharyngeal changes in children with COVID-19 might be associated with MIS-C.[6] It has been stated that during the clinical course of COVID-19 and MIS-C, xerostomia and taste disorder, swelling of the gingiva, oral mucosal irritation, strawberry tongue, redness/swelling of the lips, and white lesions on the tongue surface may accompany the disease. Moreover, these intraoral lesions were more frequent in MIS-C.[5-7,10,14] Xu et al.,[16] in their study on patients with SARS-CoV-2 infection, demonstrated the presence of high levels of ACE-2 in the oral mucosa, especially in the tongue and salivary glands. The interaction between SARS-CoV-2 and ACE-2 might be associated with changes in the oral cavity and tongue caused by abnormal function of oral keratinocytes. Depending on these changes, the patient may experience decreased taste sensation, dry mouth, and painful ulcerations in the oral cavity.[16] Additionally, increased immune response due to the infection activates Langerhans cells and lymphocytes, leading to vasculitis and thrombocytopenia, and petechiae-like lesions that can be found on the lips, tongue, and oral mucosa.[23] In our cohort, the presence of chapped lips in children with MIS-C and COVID-19 was diagnosed by pediatricians during the first examination at the pediatric clinic, and other oral lesions were recorded. Our research team observed patients from the time of diagnosis of MIS-C; therefore, we believe that the presence of chapped lips is more likely due to MIS-C.

A recent systematic review and meta-analysis of COVID-19 patients demonstrated an increased frequency of xerostomia and aphthous lesions.[15] Similarly, both direct and indirect roles of SARS-CoV-2 in the development of oral lesions have been supported by clinical data from 47 children with MIS-C.[7] Halepas et al.[6] reported that oral and oropharyngeal findings were observed in 55.3% of the patients, edema in the labial mucosa, and hyperemia in 23 (48.9%) of the patients, strawberry tongue in 5 (10.6%) patients and other oral findings in 7 (14.9%) patients with MIS-C. In our data, similar to the published evidence, changes in the lips, gingiva, tongue, and oral mucosa of children who had MIS-C were observed at a much higher rate than in children who had COVID-19. Importantly, strawberry tongue was observed in more than 1/3 of MIS-C patients. In accordance with our findings, a recent meta-analysis conducted by Aragoneses et al.[15] stated that the tongue was the most affected region.

In addition, studies have shown that patients with poor oral hygiene (high level of dental plaque and increased number of dental caries) had more severe complications of COVID-19.[16-18] It is stated that especially the oral cavity is potentially responsible for the development of hospital-acquired pneumonia, and cariogenic bacteria on the oral biofilm may

affect the severity of COVID-19 complications, as it is a reservoir for respiratory pathogens.[9,19-22] On the oral biofilm, ACE-2 receptors on the tongue play an important role in the entry of SARS-CoV-2 into host cells, and patients with high ACE-2 expression may be more susceptible to SARS-CoV-2 infection.[9] Moumalini et al.[19] stated that one of the critical symptoms seen in SARS-CoV-2 infection is gingivitis with bleeding, interpreted as an increase in inflammation due to elevated biomarker levels (i.e. cytokine and interleukin levels). In the present study, when the question of "Does your teeth bleed while brushing?" was asked, most of the patients who had both COVID-19 (54.8%) and MIS-C (34.8%) reported having a bleeding gingiva.

It is stated that poor oral hygiene and the degree of gingival inflammation in adults may lead COVID-19 to progress more severely or to increase the infection to a higher level.[9,27,28,29] Sirin et al.[27] evaluated the relationship between the oral hygiene status and the number of dental caries and COVID-19 in 137 adult patients aged 20-65 years in their radiographic study. They stated that patients having an increased number of dental caries and periodontal disease had more severe COVID-19. As with adult patients, the poor OHI in children, intense dental plaque levels, and the excess of cavitated dental caries suggest that it may be a contributing factor for MIS-C. Although a limited number of studies have investigated the changes in oral, oropharyngeal, and tongue regions in children with COVID-19 and MIS-C, no study has shown the relationship between DMFT index and OHI. The present study demonstrated twice as high DMFT and/or dmft indices in children with MIS-C when compared to those with COVID-19.

Takahashi et al.[17,18] showed in two studies that bacteria and bacterial endotoxins increase the presence of ACE-2 receptors in patients with intense bacterial plaque. The mechanism explaining the link between dental plaque and severe COVID-19 complications is attributed to inflammation resulting from the increased level of pro-inflammatory cytokines.[18] Coke et al.[21] pointed out that there may be a link between periodontal diseases, poor oral hygiene, increased plaque levels, and the severity of COVID-19, and the detection of SARS-CoV-2 in gingival crevicular fluid supports this assumption. Yang et al.[22] showed that, in addition to improvement in oral hygiene and elimination of dental plaque, the risk of pneumonia is reduced in COVID-19 patients receiving periodontal treatment. In the present study, OHI status was higher in children with MIS-C. This finding suggests that while high plaque levels and periodontal disease are associated with the severity of COVID-19 in adult patients, high OHI values might be more related to MIS-C in children.

This study has some limitations. The study population was only selected from patients who visited a university pediatric clinic with complaints of COVID-19 and MIS-C. Patient follow-up and medical data were based on medical records from a single center rather than on a pre-standardized protocol. In addition, the present study did not include children with any systemic condition rather than MIS-C and/or COVID-19. Despite these possible limitations, this study is valuable for demonstrating the importance of oral manifestations and oral hygiene in children with COVID-19 and MIS-C. Future prospective studies with a larger sample size investigating the effects of dental treatment on both diseases are warranted to determine whether oral health status contributes to MIS-C as an exacerbation of COVID-19.

Within the limitations of the present study, it was found that the oral hygiene status of children who experienced MIS-C was inadequate when compared to those who had COVID-19. Therefore, it is vital to improve oral hygiene to reduce the bacterial load in the oral cavity and the risk of bacterial superinfection observed in this specific patient population.

Why this paper is important to pediatric dentists?

a. Oral manifestations and dental symptoms were frequent among children with MIS-C;
b. Dental professionals should be aware of MIS-C, which presents a morbidity risk for disease-associated oral manifestations;
c. Medical professionals should consider referral of this specific patient population to dental professionals.

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Where is read: Şilem Özdem ERBAŞ
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Should read: İrem Ceren ERBAŞ

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