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ORIGINAL ARTICLE

Oral manifestations in patients with dengue. a forgotten and neglected disease. cross-sectional study. Salta, Argentina 2024

Ignacio Molina Ávila[1]*, Astrid Müller[2], Karina Cordero-Torres[3], Juan Pimentel Solá[4], Eduardo David Piemonte[5]

Abstract:

Objective: This study sought to identify the oral symptoms in dengue patients treated at Señor del Milagro Hospital in Salta, Argentina, from April 1 to April 30, 2024. **Methods:** A descriptive, observational cross-sectional study included a non-probabilistic sample of 57 patients aged over 15, diagnosed with dengue according to the OPS 2023 guidelines. Data on variables like age, sex, hematocrit, hemoglobin, platelet and white blood cell counts, along with the occurrence of bleeding, petechiae, and dysgeusia were documented. **Results:** Among the 57 patients, 61.4% were female and 38.6% were male, with a mean age of 35 years (range: 15-68 years). Seventy percent of the patients had dysgeusia, whereas fifty percent demonstrated gingival hemorrhage. Only 3.5% exhibited no oral symptoms. A minor leukocytosis was noted in patients with dysgeusia (2900/mm3 leukocytes) compared to subjects without dysgeusia (3240/mm3 leukocytes), although without significant differences (p=0.19), whereas gingival bleeding and the presence of petechiae were substantially correlated with platelet count (p=0.047). **Conclusions:** This study underscores the occurrence of oral manifestations in dengue patients, highlighting the necessity of their assessment in dental practice within endemic regions and advocating for additional research on these manifestations in subsequent studies.

Keywords: Aedes aegypti; Oral manifestation; Dysgeusia.

INTRODUCTION

Dengue, a viral illness predominantly transmitted by the Aedes aegypti mosquito, is a significant public health concern globally, affecting numerous regions[1-3]. The etiological agent of this disease is the dengue virus (DENV), classified under the Flavivirus genus. The virus comprises four unique serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), each capable of inducing the pathology in humans. The virus is transmitted via the bite of the infected Aedes aegypti[4].

Dengue, with its three stages of severity, poses a significant threat. The natural history of this disease begins with the inoculation of the virus via the bite of an infected mosquito. The symptoms emerge following an incubation period of 4 to 10 days and typically have a self-limiting trajectory. Some instances may advance to more severe forms, posing possible life-threatening problems. Dengue symptoms include fever, nausea, vomiting, and rash (probable dengue), severe abdominal pain, mucosal bleeding, hepatomegaly, and persistent vomiting (dengue with warning signs). More advanced forms may present with shock, fluid accumulation leading to respiratory failure, severe hemorrhage, and significant organ involvement affecting the liver, heart, central nervous system, and other organs (severe dengue)[2,5,6].

Statement of Clinical Significance
Oral manifestations are common in dengue, with those associated with coagulation disorders due to low platelet count and immunosuppression being more frequent. These findings emphasize the importance of incorporating oral evaluations in dengue management, especially in endemic regions, to enhance patient care. Further research is needed to deepen understanding of these manifestations.

The immunopathogenic pathways of dengue infection are typically linked to changes in endothelial microvascular permeability and thromboregulatory

[1]Dr. Arturo Oñativia Hospital – Salta, Argentina.
[2]Primary Care Center Laprida – Chubut, Argentina.
[3]Universidad de Valparaíso, Faculty of Dentistry – Valparaíso, Chile.
[4]Señor del Milagro Hospital Salta – Salta, Argentina.
[5]Universidad Nacional de Córdoba, Faculty of Dentistry – Córdoba, Argentina.
***Correspondence to:** imolinaavila77@gmail.com
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systems, leading to an elevated rate of protein and plasma leakage. It has been proposed that the activation of endothelial cells by monocytes, T cells, the complement system, and numerous inflammatory chemicals facilitates plasma leakage, which is related to favorable rather than detrimental effects on endothelial cells. Thrombocytopenia may develop from disruptions in megakaryocytopoiesis due to infections of human hematopoietic cells and compromised progenitor cell proliferation, culminating in platelet dysfunction, destruction, or consumption, which can lead to extensive bleeding[7].

The diagnosis of dengue relies on assessing clinical symptoms, epidemiological history, and laboratory tests, including viral detection using molecular techniques like PCR and identifying particular antibodies through serological assays like ELISA. Despite medical advancements, there exists no targeted treatment for dengue; disease care emphasizes symptomatic alleviation and complication prevention, highlighting the urgent need for further research and development in this area[4,8,9].

This disorder does not specifically affect any age, sex, or race; nonetheless, children and young adults are more susceptible to this disorder due to prolonged exposure to endemic regions and their underdeveloped immunity. The prevalence of the disease fluctuates based on factors such as population density, housing conditions, and access to medical care, predominantly occurring in endemic locations, particularly in tropical and subtropical countries characterized by warm and humid temperatures.

The World Health Organization (WHO) estimates that almost 390 million individuals are impacted yearly, with nearly half of the global population at risk[10]. In recent years, Argentina has had a notable rise in dengue infections, presenting as an endemic disease with seasonal outbreaks, particularly in summer. The nation's northern regions, including Salta, Jujuy, and Misiones, see a greater prevalence owing to their subtropical temperature and the availability of appropriate transmission vectors. Nonetheless, there has been a rise in the prevalence of dengue in several regions of the country in recent years[11].

Besides gingival bleeding, the most commonly documented oral signs of dengue include petechiae, ecchymosis, erythema, and dysgeusia[12]; however, descriptive investigations on these manifestations are few. This research aims to discover oral symptoms in dengue patients receiving treatment at the Stomatology Unit at Señor del Milagro Hospital in Salta, Argentina, throughout a designated timeframe. The study seeks to address a deficiency in scientific understanding of this subject and enhance public health by offering pertinent information to prevent and manage this condition.

MATERIALS AND METHODS

A descriptive observational cross-sectional study was performed in the Stomatology Unit of Señor del Milagro Hospital, which provides referral services in infectious diseases and stomatology for the province of Salta, Argentina. The study group comprised 57 patients over 15 years identified with dengue by the emergency medical service. The patients were examined by professionals from the Stomatology Service and assesment were permormed by two trained stomatologist, from April 1 to April 30, 2024. The study protocol, designated as protocol number 8540160524, received evaluation and approval from the Research Committee of Señor del Milagro Hospital, assuring adherence to ethical standards following the Declaration of Helsinki, and securing signed informed permission from all participants.

The individuals involved in the study met the classification criteria established by the 2023 WHO standards related to dengue case definitions[10].

The documented data comprised age, sex (female/male), and laboratory test results (complete blood count and coagulation profile) obtained from the patients' medical records. A distinct number was provided to each medical record to safeguard the security and privacy of participants.

The documented variables were characterized by absolute and relative frequencies for qualitative variables, or by mean, range, and standard deviation for quantitative data. The statistical analysis correlating oral manifestations with laboratory parameters was conducted using non-parametric Wilcoxon test, with a significance level set at 0.05, utilizing Infostat 2020 software.

RESULTS

In this study, 57 patients were recruited, with 35 (61.4%) women and 22 (38.6%) men. The mean age of the sample was 35,4 years, ranging from 15 to 68 years. The mean hematocrit readings were 39.95%, according to the typical variations between females and males. 88% of the patients exhibited a leukocyte count below 4000 per mm^3. The mean platelet count was 63.450 per mm^3 (Table 1).

Table 1. Demographic and hematological characteristics.

n	57
Sex (%)	
Female	35 (61.4)
Male	22 (38.6)
Age	
Mean (SD)	35,4 years (13.7)
Range	15–68 years
Haematocrit	
Mean (SD)	39,95% (6.07)
Range	22–50%
Leukocytes	
Mean (SD)	3000/mm^3 (910)
Range	1400–5200/mm^3
≥4000	7 (12%)
<4000	50 (88%)
Platelets	
Mean (SD)	63450/mm^3 (41700)
Range	3000–204000/mm^3
≥150000	3 (5%)
<150000	54 (95%)

SD: standard deviation.

Upon examination of the oral cavity, only two patients (3.5%) exhibited no lesions. Conversely, 70% of the patients reported dysgeusia, and almost 50% of the sample experienced gingival bleeding, with acute necrotizing ulcerative gingivitis (ANUG) observed in 16% of the cases (Figure 1). Additional clinical observations comprised xerostomia, petechiae, erythematous candidiasis, acute abscesses, and temporomandibular joint pain. 16% exhibited severe lymphadenopathy (Table 2). Clinicians established the diagnosis of necrotizing ulcerative gingivitis through clinical evaluation and direct microscopic inspection of swab samples, demonstrating the existence of fusospirochetal connections.

The analysis of the relationship between oral factors and several clinical and laboratory variables revealed a higher incidence of leukopenia in patients with dysgeusia than in those without; however, this difference did not achieve statistical significance. Patients with gingival bleeding and petechiae or ecchymosis had lower platelet counts, but without statistically significant differences. Patients with xerostomia had higher platelet count, with *p*-value close to statistical significance (p=0.053) (Table 3).

Figure 1. (**A**) Male, 25 years old, spontaneous bleeding, dysgeusia. Hematocrit 45.7%, lymphocytes 2580/mm^3, platelets 74,000/mm^3; (**B**) Male, 16 years old, spontaneous bleeding, papillary necrosis, petechiae, dysgeusia. Lymphadenopathy. Hematocrit 38.6%, lymphocytes 2510/mm^3, platelets 61,000/mm^3; (**C**) Female, 30 years old, spontaneous bleeding, dysgeusia. Hematocrit 43%, lymphocytes 3700/mm^3, platelets 58,000/mm^3; (**D**) Male, 30 years old, papillary necrosis, Hematocrit 37.7%, lymphocytes 2140/mm10^3, platelets 62400/mm^3.

Table 2. Oral manifestations in dengue patients.

Manifestation	n	%
Dysgeusia	40	70
Gingival bleeding	28	49
Xerostomia	17	30
Petechiae/ecchymosis	14	24
Acute necrotizing ulcerative gingivitis	9	16
Lymphadenopathy	9	16
Candidiasis	3	5
Erythema	2	3,5
Erosions	2	3,5
Acute abscess	1	1,7
Temporo mandibular joint pain	1	1,7
Without manifestations	2	3,5
Total	57	100

Table 3. Association between clinical manifestations and hematological variables.

Clinical manifestation	Haematological variable	p-value*
Female sex	Haematocrit 38,37%	**0.0028**
Male sex	Haematocrit 42,46%	
Without dysgeusia	3240/mm^3 leukocytes	0.118
With dysgeusia	2900/mm^3 leukocytes	
Without gingival bleeding	72460/mm^3 platelets	0.167
With gingival bleeding	54120/mm^3 platelets	
Without petechiae/ecchymosis	67920/mm^3 platelets	0.330
With petechiae/ecchymosis	49710/mm^3 platelets	
Without xerostomia	57270/mm^3 platelets	0.053
With xerostomia	78000/mm^3 platelets	

*Wilcoxon test. Bold indicates statistically significant p-values.

DISCUSSION

Neglected and untreated diseases are infections that primarily impact on the world's poorest and most vulnerable communities. Their scope includes diseases such as Chagas, dengue, leishmaniasis, leptospirosis, malaria, schistosomiasis, lymphatic filariasis, helminthiasis, echinococcosis, onchocerciasis, rabies, trachoma, Buruli ulcer, deep mycoses, and yaws, many of which are endemic to the Americas[10]. Worldwide public health faces considerable challenges due to dengue, especially in endemic regions like Salta province, Argentina, where this study was conducted.

Despite its widespread proliferation in numerous places and the mouth cavity serving as a site for presenting specific dengue symptoms, little research has concentrated on its oral manifestations. Most prior research has concentrated on the systemic signs of the disease, resulting in a considerable deficiency in the comprehension of dengue's impact on the oral cavity. The review by Pedrosa et al. encompassed 10 case reports on oral lesions and 15 descriptive studies, most of which were not intended to document mucocutaneous lesions, including those of the oral mucosa[12]. This deficiency constitutes a considerable constraint in comprehending the effects of this disease on the human body, underscoring the necessity for more comprehensive research on the oral manifestations of this infection[12].

Oral lesions were identified in 96.5% of the patients examined, a significantly greater prevalence than reported in existing literature. Fera documented oral lesions in 31% of his patients[13], Roopashri et al.[7] noted a prevalence of 30%, and Anekar et al.[1] observed only 20%. Gingival hemorrhage was noted in 49% ancies may indicate variations in the studied populations, methodologies utilized, or the clinical manifestations of dengue influenced by geographical or genetic factors.

Little scientific literature identifies the common oral signs of dengue as dysgeusia, ulcers, erosions, petechiae, xerostomia, and gingival bleeding. Moreover, there are case reports indicating diseases that have emerged during or after dengue, exploiting the systemic decline experienced by the patient.

In this research, dysgeusia was the most prevalent sign, occurring in 70% of cases, a phenomenon seldom documented in literature. Pedrosa et al.[12] and Fera et al.[13] identified it as the most prevalent mucocutaneous manifestation, occurring at a frequency of 48.5%, which is significantly lower than our findings. This discrepancy may arise from Fera et al. including patients with both oral and other mucocutaneous symptoms. Also, it may be associated with geographical differences, prior immunity, and local clinical practices[13]. The pathophysiological process behind dysgeusia remains unexplained, and various causes may be suggested. One possibility is the neurosensory abnormalities caused by the virus, while another may be merely a result of dehydration and xerostomia.

Secondly, gingival hemorrhage was noted in 49% of the patients. This study associates the distinctive thrombocytopenia of dengue with its classic symptoms, indicating a potential clinical marker for identifying the hemorrhagic phase of the disease. In our investigation, the incidence of gingivorrhagia exceeded the figures documented in the systematic review by Pedrosa et al., which revealed a range "In this investigation, dysgeusia

was the most prevalent of 3.5 to 35%[12]. These disparities may be ascribed to discrepancies in clinical care, comorbidities, other contextual factors, and differences in case recording methods.

Mithra et al. reported a dengue hemorrhagic fever case with prominent oral findings, including gingival bleeding, hemorrhagic plaques, erythematous erosions, tonsillar inflammation and xerostomia[14], in our series, xerostomia was observed in 30% of patients. This symptom may be categorized as an indication of dehydration commonly observed in people with dengue.

One of the most documented symptoms in literature is petechiae on the oral mucosa, which is distinctly associated with hemorrhagic abnormalities in the patients. Petechiae or ecchymoses, as mucocutaneous manifestations, have been documented in over 60% of patients. However, cases of oral manifestation remain unspecified. Petechiae on the oral mucosa were observed in 24% of cases, marginally exceeding 12.5% reported by Anekar et al.[1]

The decline of the immune system due to dengue accounts for the emergence of opportunistic infections in the oral mucosa, including candidiasis. Studies report that candidiasis affects between 2% and 18% of adults who do not use dentures[15,16]. The prevalence of candidiasis among our patients was 5%, comprising instances without detachable prosthesis.

Erosions and generalized oral mucosa erythema were rare among our patients, occurring in about 3.5% of cases. These findings differ from other studies that report rates of 6%[1] or between 16% and 66%[12]. This discovery may be associated with the direct cytopathic impact of the dengue virus on oral epithelial cells and the host's inflammatory response.

Occasional oral symptoms in dengue patients have been documented, including vesicles and hemorrhagic blisters in various regions of the oral cavity[17,18], which may be associated with hemorrhagic changes. At least three instances of osteonecrosis of the jaws with unknown etiology have been linked to dengue, potentially attributable to either hemorrhagic bone infarction or the compromise of the patient's immune system[19-21]. This study could not document such lesions. The vesicles, hemorrhagic blisters, and osteonecrosis of the jaws are likely infrequent symptoms in dengue patients and necessitate far larger population samples than those in the current investigation for detection.

A significant result in our research is the identification of oral symptoms not previously documented in the literature, including ANUG and painful lymphadenopathy. ANUG instances were validated via direct microbiological testing, potentially linked to transitory immunosuppression and thrombocytopenia, alongside a decline in oral hygiene practices resulting from the patient's significant debilitation. Painful lymphadenopathies, albeit less common, may be linked to the host's inflammatory response. These discoveries underscore the necessity for further extensive research to investigate these connections in greater depth.

Previous international research, including one conducted at the University Hospital of La Réunion, France, examined the incidence of mucocutaneous symptoms and their correlation with purpura in patients with PCR-confirmed dengue. It is presumed that they would be associated with severe disease manifestations[22]. In a cross-sectional study of 200 confirmed dengue cases in Sullia (India), the authors reported a mean platelet count of 94 890 cells/mm^3 but did not present detailed subgroup analysis of leukocyte counts[1]. Our patients' platelet and leukocyte count correspond with those documented in the literature on dengue, confirming that thrombocytopenia and leukopenia are hallmark features of the infection[1]. The patients exhibited no substantial changes in hematocrit, likely because they had commenced treatment when this data was collected. Certain clinical manifestations have been demonstrated to correlate with specific laboratory values in our investigation. Regardless of gingival bleeding and petechiae or ecchymoses, patients exhibited platelet counts below normal thresholds. Gingival bleeding and petechiae or ecchymosis did not correlate significantly with a reduced platelet count, although this could be due to the small number of cases included. Based on these results, it is not possible to use oral symptoms associated with hemorrhagic diseases as a parameter to classify the severity of the clinical picture in patients with dengue[7].

This research, undertaken during an outbreak in Salta, Argentina, enhances the existing knowledge on oral symptoms of dengue by discovering a broader spectrum of manifestations and their correlation with specific laboratory data. The observation that 70% of patients had dysgeusia and 50% exhibited gingival bleeding indicates potential for research to ascertain the diagnostic and prognostic significance of these symptoms[7].

Our study has limitations, including a reduced sample size, the exclusion of patients under 15 years of age, and the absence of patient follow-up. The latter would be essential to match the patient's progression with the oral signs. Future multicentric and longitudinal research may yield a more rigorous and thorough assessment of these manifestations across many epidemiological scenarios.

CONCLUSION

Oral manifestations of dengue are very frequent and can be related to the direct effects of the virus or to the systemic changes that the patient suffers, especially in relation to hemorrhagic disorders, dehydration, and immunosuppression. Longitudinal studies are needed to evaluate whether oral manifestations are useful for early diagnosis or prognosis of dengue.

AUTHORS' CONTRIBUTIONS

IMA: Conceptualization, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. AM: Investigation, Validation, Writing – original draft, Writing – review & editing. KCT: Formal analysis, Supervision, Writing – review & editing. JPS: Investigation, Resources, Validation, Writing – original draft, Writing – review & editing. EP: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Ethics approval: This Project follows the principles of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The study protocol was approved by the advisory committee on teaching and research (CADI) of the Señor del Milagro Hospital, Salta, Argentina (reference number 85/2024).

Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work the authors used ChatGPT in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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