J Oral Med Oral Surg 2022;28:45
https://doi.org/10.1051/mbcb/2022028

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Original Research Article

Acute periapical abscesses in patients with herpes simplex type 1 and herpes zoster

Ilan Rotstein[1,*], Joseph Katz[2]

[1] University of Southern California, Los Angeles, CA, USA
[2] Department of Oral Diagnostic Sciences, University of Florida College of Dentistry, Gainesville, FL, USA

(Received: 19 July 2022, accepted: 14 September 2022)

Keywords:
Apical abscess / endodontics / herpes simplex / herpes zoster / periapical abscess

Abstract – Aim: To assess the prevalence of acute periapical abscesses (PAs) in patients infected with herpes simplex type 1 (HS-1) and herpes zoster (HZ). **Materials and methods**: Integrated data of hospital patients was used. History of HS-1 and HZ diagnosis was retrieved by searching the appropriate query in the database. All cases were diagnosed for acute PAs by calibrated dentists in a hospital setting for patients admitted to urgent care. Diagnosis was made based on clinical examination and imaging data confirming the diagnosis of acute PAs without sinus tract. The odds ratio (OR) for the prevalence of acute PAs and its association with history of HS-1 and HZ were then calculated. **Results**: The prevalence of acute PAs in patients with a history HS-1 was 2.43% as compared to 0.59% in the general patient population of the hospital. The OR was 4.12 and the difference in prevalence was statistically significant ($p < 0.0001$). The prevalence of acute PAs in patients with a history HZ was 2.78% as compared to 0.59% in the general patient population of the hospital. The OR was 4.71 and the difference in prevalence was statistically significant ($p < 0.0001$). **Conclusions**: Under the conditions of this study, it appears that the prevalence of acute PAs is significantly higher in patients with a history of HS-1 and HZ infections and may warrant an antiviral therapy in certain resistant periapical abscesses.

Introduction

Herpesviruses are common viruses capable to infect human populations [1]. At least eight species of herpesviruses have been identified to infect humans, and are classified into 3 subfamilies: alpha-herpesvirinae, beta-herpesvirinae and gamma-herpesvirinae. The alpha-herpesvirinae subfamily includes herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2) and the varicella zoster virus (VZV). The beta-herpesvirinae subfamily includes human cytomegalovirus (HCMV), human herpes virus 6, and human herpesvirus 7. The gamma-herpesvirinae subfamily includes viruses linked to cancer, Epstein-Barr virus (EBV) and Kaposi Sarcoma-associated herpesvirus [1,2]. Herpesviruses are very adaptable to life-long infection of their human hosts and can be considered a component of the human microbiome [3].

Herpes simplex type 1 (HS-1) caused by HSV-1 is a common infection affecting the host's immune system. Following a first exposure, susceptible individuals develop "primary" infection and produce antibodies to the virus. In such cases, it is most commonly encountered in the oral cavity [4]. Most previously exposed people present with latent virus that can be reactivated when the body' immune system goes under duress [5]. After reactivation, shedding of HSV-1 can occur asymptomatically in saliva [6]. At least 70% of the population shed HSV-1 asymptomatically in multiple intraoral sites at least once a month. Some individuals may shed HSV-1 more than 6 times per month [6].

Demographic factors may affect the acquirement of HS-1 infection. In third world countries, circa 30% of children acquire the infection by age 5 and more than 70% when reaching adulthood. In more developed countries, the incident is lower by 10–15% [5]. It has also been reported that the incidence of HS-1 infection among university students may reach up to 10% per year [7]. While very common, HS-1 infection is rarely fatal.

Herpes Zoster (HZ) is caused by VZV and is a significant medical condition causing acute and chronic pain and often neuronal destruction thus reducing the quality of life of the affected individuals [8]. It can affect individuals of any age although it is more common in older adults, individuals with immunocompromised conditions, and in patients receiving long-term treatment with immunosuppressants [9]. Signs and symptoms appear following reactivation of a dormant VZV infection. The most common complication associated with HZ is a debilitating post-herpetic neuralgia. Risk factors and potential health complications associated with HZ depend on the patient's age, immunity, and the time elapsed from initiation of the condition to treatment [9].

* Correspondence: ilan@usc.edu

Acute periapical abscess is an inflammatory reaction to pulpal infection and necrosis characterized by rapid onset, spontaneous pain, tenderness of the tooth to pressure, pus formation and swelling of the associated tissues [10]. Periapical abscesses (PAs) present a serious health risk to patients and requires expeditious and efficient treatment. It has been reported that in the United States, more than 400,000 emergency patient visits were due to either pulpal or periapical diseases resulting in medical charges totaling more than $160 million [11]. More than 60,000 hospitalizations were primarily attributed to acute PAs [12].

Several studies explored the potential association between endodontic abscesses and HS and HZ, with conflicting results. Chen *et al.* [13] collected samples from patients presented with PAs and cellulitis of endodontic origin. Following analysis of the samples with polymerase chain reaction using virus-specific primers and DNA isolated from cell-free abscess fluid, one sample was found to be positive to HSV-1. No evidence for presence of VHZ virus was found [13]. Nishiyama *et al.* [14] assessed the occurrence and the combinations among HS-1 and 3 types of oral microorganisms in patients with chronic periodontitis and necrotic pulps. HS-1 was observed in one patient with periodontitis and in another patient with necrotic pulp (11). Ferreira *et al.* [15,16] reported that several specimens collected from patients with acute PAs were positive to VHZ virus. In addition, several case reports suggested a possible link between VHZ virus and the presence of apical pathosis, and root resorption [17–20]. It has also been reported that VHZ may cause alveolar bone necrosis [21]. However, studies on large cohort of patients are limited.

Exploring the possible link between the herpesvirus family and periapical abscesses may have clinical significance in identifying antiviral treatments as an aid for periapical infections. The aims of this cross-sectional study were, therefore, to assess the prevalence of acute PAs in patients with a history of HS-1 and HZ infections and to compare between genders, ethnicities, and age groups.

Materials and methods

The University of Florida (UF) Integrated Data (IDR) i2b2, supported by the National Institute of Health (NIH) and the UF Health Office of the Chief Data Officer, for the period from October 2015 to June 2021 was used. The study was in compliance with the UF Institutional Review Board (IRB), ethics, and privacy rules.

Data aggregate from inpatients and outpatients visiting the UF Health Center were recorded using the electronic patient record Epic (epic.com). Epic is the preferred electronic medical record system used by more than 250 health care organizations in the USA. More than 50% of the USA population has their medical records in an Epic system.

The different diagnoses were coded using the international coding systems ICD 10. The ICD system requires that all HIPAA-covered entities implement the ICD-10-CM diagnosis code set. Medicaid is a HIPAA entity, as are medical and dental clinics. The ICD coding system has also been adopted by the American Dental Association.

The patient population analyzed was mixed, presenting with different disease conditions including acute PAs without sinus (ICD 10 K04.7). All cases were diagnosed for acute PAs by calibrated dentists in a hospital setting for patients admitted to urgent care. Diagnosis was made based on clinical examination and imaging data confirming the diagnoses of acute PAs without sinus tract.

Inclusion criteria included the corresponding diagnostic code for PAs without sinus (ICD 10 K04.7). There was no exclusion criteria since all codes were computerized, and specific diagnoses of acute PAs in the total hospital patient population were searched using the appropriate ICD 10 code. History of HS-1 and HZ diagnosis was retrieved by searching the appropriate query in the database.

The odds ratio (OR) for the prevalence of acute PAs and its association with history of HS-1 and HZ were calculated with a 95% confidence interval and the statistical difference between the study groups was assessed using MedCalc software (medcalc.org). A standard normal deviate (z-value) was calculated as follows: ln(OR)/SE{ln(OR)}. The p-value was the area of the normal distribution that falls outside $\pm z$ [22]. A value of $p < 0.05$ was considered statistically significant.

Results

The demographics of the hospital patient population studied are summarized in Table I. The total hospital patient population studied was 1,213,693; 46.2% males and 53.8%% females (Tab. I). Out of the total hospital patient population, 0.77% was diagnosed with a history of HS-1. Males were more affected than females by 2.5 folds. Whites were more affected than African Americans by almost 3.5 folds. Whites were more affected than African Americans combined with other ethnicities by 2 folds. Children were more affected than adults by 6.5 folds (Tab. I).

Out of the total hospital patient population, 0.43% was diagnosed with a history of HZ. Females were more affected than males by 1.7 folds. Whites were more affected than African Americans by more than 5 folds. Whites were more affected than African Americans combined with other ethnicities by more than 3 folds. Adults over the age of 18 were exclusively affected (Tab. I).

Out of the total hospital patient population, 0.59% was associated with PAs (Tab. I). Out of the patients with a history of HS-1, 2.43% were associated with acute PAs. Females were more affected than males and the difference was statistically significant ($p < 0.01$). Whites were more affected than African Americans and the difference was statistically significant ($p < 0.01$). Children were significantly more affected than adults ($p < 0.01$) (Tab. I).

Out of the patients with a history of HZ, 2.78% were associated with acute PAs. HZ patients with PAs were exclusively adults. Females were more affected than males, however, the difference was not statistically significant. Whites

Table I. Demographics of the hospital patient population studied. Pas = periapical abscesses; HS-1 = Herpes Simplex type 1; HZ = Herpes Zoster.

	Acute Pas (n = 7172)	HS-1 (n = 9364)	HZ (n = 5281)	Acute PAs and HS-1 (n = 228)	Acute PAs and HZ (n = 147)	Total patients (n = 1,213,693)
Males	3152 (44%)	6721 (71.8%)	1966 (37.2%)	* 61 (26.8%)	# 60 (40.8%)	560,637 (46.2%)
Females	4020 (56%)	2643 (28.2)	3315 (62.8)	167 (73.2%)	87 (59.2%)	653,056 (53.8%)
Whites	4079 (57%)	6305 (67.3%)	4019 (76%)	** 118 (51.7%)	## 94 (64%)	577,991 (47.6%)
African Americans	2524 (35%)	1819 (19.5%)	736 (14%)	100 (43.9%)	44 (30%)	126,929 (10.5%)
Other Ethnicities	569 (8%)	1240 (13.2%)	526 (10%)	10 (4.4%)	9 (6%)	508,773 (41.9%)
Adults (>18 years)	6244 (87%)	1240 (13.2%)	5281 (100%)	*** 10 (4.4%)	### 147 (100%)	1,035,064 (85.3%)
Children (<18 years)	928 (13)	8124 (86.8%)	0 (0%)	218 (95.6%)	0	178,629 (14.7%)

* Comparison between genders in the acute PAs and HS-1 group. Chi-square statistic is 34.6544; p-value = 0.00001. Significant at $p < .05$.
** Comparison between Whites and African Americans in the acute PAs and HS-1 group. Chi-square statistic is 114.5746; p-value = 0.00001. Significant at $p < .05$.
*** Comparison between adults and children in the acute PAs and HS-1 group. Chi-square statistic is 1187.5109; p-value = 0.00001. Significant at $p < .05$.
# Comparison between genders in the acute PAs and HZ group. Chi-square statistic is 1.7093; p- value = 0.19. Not significant at $p < .05$.
Comparison between Whites and African Americans in the acute PAs and HZ group. Chi-square statistic is 17.9965; p-value = 0.00002. Significant at $p < .05$.
Comparison between adults and children in the acute PAs and HZ group. Chi-square statistic is 6.6318; p-value = 0.01. Significant at $p < .05$.

Table II. Prevalence of acute periapical abscesses (PAs) in herpes simplex type 1 (HS-1) and herpes zoster (HZ) patients. OR = Odds Ratio; CI = Confidential Interval.

	HS-1	HZ
Acute PAs	228	147
Number of patients	9,364	5,281
OR	4.12	4.71
95% CI	3.60–4.70	3.99–5.55
p-value	<0.0001	<0.0001

were more affected than African Americans and the difference was statistically significant ($p < 0.01$). Adults were significantly more affected than children ($p < 0.01$) (Tab. I).

The prevalence of acute PAs in patients with a history of HS-1 was 2.43% as compared to 0.59% in the general patient population of the hospital (Tab. II). The OR was 4.12 and the difference in prevalence was statistically significant ($p < 0.0001$) (Tab. II).

The prevalence of acute PAs in patients with a history of HZ was 2.78% as compared to 0.59% in the general patient population of the hospital (Tab. II). The OR was 4.71 and the difference in prevalence was statistically significant ($p < 0.0001$) (Tab. II).

Discussion

The results of the present cross-sectional study indicate that the odds for developing acute PAs may be higher in patients with a history of HS-1 and HZ infections. In both conditions, whites were significantly more affected than African Americans. Females were more affected than males in both conditions, however, the difference was statistically significant only for the HS-1 patients. As expected, HS-1 is mainly affecting younger individuals, whereas HZ affects mainly adults. These demographic outcomes are consistent with the current literature that asserts an early impact of HSV-1 at childhood and a later onslaught of the VZV during the 6th and 7th decade of life [23]. However, this is the first cross-sectional study done on a large hospital patient population demonstrating an association between Herpes virus family members and acute PAs.

As part of the characteristics of the human herpesvirus family, HSV-1 and VZV are DNA viruses [24]. After the primary infection, these viruses can become dormant and can be reactivated when the immune system is compromised, resulting in significant damage to organs such as liver, kidney and brain [23,25]. HSV-1 infects most humans, attaining 90% prevalence by the sixth decade of life. Infection is life long, as the virus resides in the trigeminal ganglia of the peripheral nervous system in latent form with viral genome but no virions present. Reactivation leads to viral replication and acute infections known as herpes labialis, commonly referred to as cold sores [5].

The exact mechanism by which herpesvirus infection causes periapical abscess is not completely clear. It has been suggested that herpesviruses don't possess the ability to cause dental abscesses on their own, however, they can adversely affect host resistant factors and serve as a pathway for existing bacterial pathogens to invade the affected site [15]. The process may include initial root canal contamination by microorganisms causing periapical inflammation. Consequently, host defense

cells, infected by herpesviruses, are activated and attracted to the site of inflammation. Reactivated herpesviruses can further reduce the host resistance in situ and facilitate further tissue destruction by the invading microorganisms [26,27]. An active herpesvirus infection is a potent stimulant of cellular immunity. Pro-inflammatory cytokines induced by herpesvirus infection may activate matrix metalloproteinases and osteoclastic activity, leading to breakdown of tissues surrounding the root, including alveolar bone [28].

It has been demonstrated that herpesvirus infection is associated with periapical disease [27]. Furthermore, a recent study assessed the efficacy of valacyclovir, an anti-herpesvirus medication, for pain control associated with acute PA [29]. It was found that there was a statistically significant reduction in pain levels when valacyclovir was used as compared to placebo controls. This supports our findings that viruses from the herpesvirus family can be associated with acute periapical disease. Oral healthcare providers should be aware of such potential association and consider using supplementary antiviral therapy in certain resistant periapical infections.

Several limiting factors should be considered when extrapolating the data of this cross-sectional study. First, the patient population examined may have had additional underlying systemic or dental conditions. However, those conditions were not included for the purpose of this study. Second, only the presence of acute PAs in the period of the study was analyzed. Whether the periapical pathoses were active or in a process of healing is unknown. Third, socio-economic factors may affect the decision of certain patients to seek medical and dental care in a specific location. Therefore, the prevalence of PAs in this study may also reflect social-economic disparities.

In conclusion, the results of the present study indicate that the prevalence of acute PAs is significantly higher in patients with a history of HS-1 and HZ infections. The exact cause and effect require further exploration.

Authors contributions

Ilan Rotstein: Conception and design of the study, Analysis of data, Drafting of the article, Finalizing the article.

Joseph Katz: Conception and design of the study, Acquisition of data, Review of the article, Finalizing the article.

Ethics approval and informed consent

All the procedures performed in our study followed the ethical standards of the institutional research committee and Privacy rules for research on IRB approved de-identified data sets. Approval date: April 6, 2021.

Conflicts of interest

The authors declare they have no conflicts of interest in relation to this article.

Funding

This research did not receive any specific funding.

References

1. Sadeghipour S, Mathias RA. Herpesviruses hijack host exosomes for viral pathogenesis. Semin Cell Dev Biol 2017;67:91–100.
2. Slots J, Slots H. Periodontal herpesvirus morbidity and treatment. Periodontology 2000 2019;79:210–220.
3. Dreyfus DH. Herpesviruses and the microbiome. J Allergy Clin Immunol 2013;132:1278–1286.
4. Heling I, Morag-Hezroni M, Marva E, Hochman N, Zakay-Rones Z, Morag A. Is herpes simplex virus associated with pulp/periapical inflammation? Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:359–361.
5. Whitley RJ, Roizman B. Herpes simplex virus infections. Lance 2001;357:1513–1518.
6. Miller CS, Danaher RJ. Asymptomatic shedding of herpes simplex virus (HSV) in the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:43–50.
7. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. Scand J Infect Dis 1990 (Suppl);69:19–36.
8. Schmader K. Herpes Zoster. Clin Geriatr Med 2016;32:539–553.
9. Koshy E, Mengting L, Kumar H, Jianbo W. Epidemiology, treatment and prevention of herpes zoster: a comprehensive review. Indian J Dermatol Venereol Leprol 2018;84:251–262.
10. Glossary of endodontic terms. American Association of Endodontists, 10th edn. Chicago IL, 2020, p. 4.
11. Nalliah RP, Allareddy V, Elangovan S, Karimbux N, Lee MK, Gajendrareddy P, *et al.* Hospital emergency department visits attributed to pulpal and periapical disease in the United States in 2006. J Endod 2011;37:6–9.
12. Shah AC, Leong KK, Lee MK, Allareddy V. Outcomes of hospitalizations attributed to periapical abscess from 2000 to 2008: a longitudinal trend analysis. J Endod 2013;39:1104–1110.
13. Chen V, Chen Y, Li H, Kent K, Baumgartner JC, Machida CA. Herpesviruses in abscesses and cellulitis of endodontic origin. J Endod 2009;35:182–188.
14. Nishiyama SA, Nakano V, Velásquez-Melendez G, Avila-Campos MJ. Occurrence of herpes simplex virus 1 and three periodontal bacteria in patients with chronic periodontitis and necrotic pulp. Can J Microbiol 2008;54:326–330.
15. Ferreira DC, Paiva SS, Carmo FL, Rôças IN, Rosado AS, Santos KR, *et al.* Identification of herpesviruses types 1 to 8 and human papillomavirus in acute apical abscesses. J Endod 2011;37:10–6.
16. Ferreira DC, Rôças IN, Paiva SS, Carmo FL, Cavalcante FS, Rosado AS, *et al.* Viral-bacterial associations in acute apical abscesses. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:264–271.
17. Ramchandani PL, Mellor TK. Herpes zoster associated with tooth resorption and periapical lesions. Br J Oral Maxillofac Surg 2007;45:71–73.
18. Patel K, Schirru E, Niazi S, Mitchell P, Mannocci F. Multiple apical radiolucencies and external cervical resorption associated with varicella zoster virus: a case report. J Endod 2016;42:978–983.
19. Talebzadeh B, Rahimi S, Abdollahi AA, Nouroloyuni A, Asghari V. Varicella zoster virus and internal root resorption: a case report. J Endod 2015;41:1375–1381.

20. Gupta S, Sreenivasan V, Patil PB. Dental complications of herpes zoster: two case reports and review of literature. Indian J Dent Res 2015;26:214–219.
21. Mendieta C, Miranda J, Brunet LI, Gargallo J, Berini L. Alveolar bone necrosis and tooth exfoliation following herpes zoster infection: a review of the literature and case report. J Periodontol 2005;76:148–153.
22. Sheskin DJ. Handbook of parametric and nonparametric statistical procedures. 5th edn, Chapman & Hall/CRC, Boca Raton, FL, 2011, pp. 761–804.
23. Mitchell BM, Bloom DC, Cohrs RJ, Gilden DH, Kennedy PG. Herpes simplex virus-1 and varicella-zoster virus latency in ganglia. J Neurovirol 2003;9:194–204.
24. Ouwendijk WJ, Laing KJ, Verjans GM, Koelle DM. T-cell immunity to human alphaherpesviruses. Curr Opin Virol 2013;3:452–460.
25. Harris SA, Harris EA. Herpes simplex virus type 1 and other pathogens are key causative factors in sporadic Alzheimer's disease. J Alzheimers Dis 2015;48:319–353.
26. Contreras A, Umeda M, Chen C, Bakker I, Morrison JL, Slots J. Relationship between herpesviruses and adult periodontitis and periodontopathic bacteria. J Periodontol 1999;70:478–484.
27. Sabeti M, Slots J. Herpesviral-bacterial coinfection in periapical pathosis. J Endod 2004;30:69–72.
28. Slots J. Periodontal herpesviruses: prevalence, pathogenicity, systemic risk. Periodontol 2000 2015;69:28–45.
29. Sabeti M, Zhong J, Hildebrandt K, Slots J. Valacyclovir in pain management of acute apical abscesses: a randomized placebo-controlled double-blind pilot study. J Endod 2021; 47:1724–1728.