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CLINICAL RESEARCH

Increased Risk for Acute Periapical Abscesses in Multiple Sclerosis Patients and the Possible Association with Epstein-Barr Virus

SIGNIFICANCE

Oral health care providers should be aware of the possible higher prevalence of acute periapical abscesses in patients with MS and a history of EBV infection.

ABSTRACT

Introduction: Multiple sclerosis (MS) is a severe inflammatory neuroimmune degenerative condition affecting more than 2 million individuals worldwide. The purpose of this study was to assess the prevalence of acute periapical abscesses in patients with MS and to evaluate whether acute periapical abscesses (PAs) are more likely to affect patients who were previously infected by Epstein-Barr virus (EBV). **Methods:** Integrated data of hospital patients were used. Data from the corresponding diagnosis codes for MS and acute PA were retrieved by querying the appropriate *International Classification of Diseases, Tenth Revision* codes in the database. **Results:** Of the total hospital patient population, 0.18% were diagnosed with a history of MS. Females were more affected than males 3.25-fold. Whites were more affected than African Americans 6-fold. Whites were more affected than African Americans combined with other ethnicities 3.6-fold. The odds ratio (OR) for acute PAs in patients with a history of MS was 2.2 ($P < .0001$). After adjustment for diabetes mellitus comorbidity, the OR for acute PAs in patients with a history of MS was 2.6. After adjustment for cardiovascular disease comorbidity, the OR for acute PAs in patients with a history of MS was 1.27. Of the patients who presented with PAs, 0.2% were diagnosed with a history of EBV infection. The OR was 3.98, and the difference in prevalence was statistically significant ($P < .0001$). **Conclusions:** Under the conditions of this cross-sectional study, it appears that the prevalence of acute PAs is higher in patients with MS and that EBV may play a role. *(J Endod 2023;49:262–266.)*

KEY WORDS

Apical disease; Epstein-Barr virus; multiple sclerosis; periapical abscess

Multiple sclerosis (MS) is a severe and debilitating disease affecting more than 2 million individuals worldwide[1,2]. This inflammatory neuroimmune degenerative condition results from a generalized destruction of the myeline sheet of affected nerves in the central nervous system. Thus far, 3 MS distinct conditions have been identified:

1. MS,
2. myelin oligodendrocyte glycoprotein antibody-associated disease, and
3. aquaporin-4 antibody-associated neuromyelitis optica spectrum disorder[3].

MS appears most often between the ages of 20 and 40 years[4], generally peaking at around age 30[5]. It has also been reported to affect younger individuals (younger than 18 years); however, it is rare[3,6]. MS is significantly more prevalent in women than in men[1,7]. Symptoms of MS can include extreme fatigue, muscular debility, generalized pain, motor disfunction, vision and speech impairment, respiratory disorder, and amnesia, among others[8,9].

The etiology of MS is not completely understood. Genetic, epigenetic, and environmental factors have been proposed as possible causes[10]. Patients with MS suffer from low bone mineral density and increased bony fractures. Osteoporosis is a major cause of morbidity and mortality and is more common in individuals with MS than in the general population[11].

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It has been suggested that patients with MS exhibit a higher tendency to be affected by certain orodental diseases[1,12–15]. McGrother et al[12] reported a statistically significant excess of dental caries among patients with MS compared with controls. Sheu and Lin[13] found an association between MS and chronic periodontitis, mainly in women. Manchery et al[1] performed a systematic review of the literature and found suggestive evidence that individuals with MS may be at higher risk for periodontal disease. Another review of randomized controlled trials, cross-sectional studies, and cohort studies found that patients with MS were at higher risk for periodontal disease and poorer oral hygiene[15].

Several studies strongly suggest that Epstein-Barr virus (EBV), a member of the herpesvirus family that is a common habitant of the oral cavity, plays a role in the evolution of MS[16,17]. A recent longitudinal analysis of more than 10 million young adults found that the risk of MS increased 32-fold after infection with EBV and was not increased after infection with other viruses[18].

EBV is a human virus that infects more than 90% of the world population during their lifetime[19]. After an acute outbreak, it persists in the body of the affected individual for the remainder of his or her life[20]. EBV has been associated with a variety of orodental pathoses such as oral malignancy[21], *Candida albicans* coinfection[22], periodontal disease[23], peri-implantitis[24], and pulpal and periapical disease[25–31]. The aims of this cross-sectional study were to assess the prevalence of acute periapical abscesses (PAs) in patients with MS and to evaluate whether acute PAs are more likely to affect patients who were previously infected by EBV.

MATERIALS AND METHODS

The University of Florida (UF) Integrated Data i2b2, provided by the UF Health Office of the Chief Data Officer for the period of June 2011 to January 2022, was used. The study was in compliance with the UF Institutional Review Board (IRB) and privacy rules for research on IRB-approved deidentified data sets. The study was exempted by the UF Health Center IRB because it did not include personal health information.

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

TABLE 1 - Demographics of the Hospital Patient Population Studied

	MS (n = 2,410), n (%)	PAs (n = 7,762), n (%)	MS + PAs (n = 28), n (%)	Total patients (N = 1,314,924), n (%)
Males	566 (23.5)	3424 (44.1)	12 (42.9)	607,104 (46.2)
Females	1844 (76.5)	4338 (55.9)	16 (57.1)	707,820 (53.8)
Whites	1890 (78.4)	4395 (56.6)	19 (67.9)	623,740 (47.4)
African Americans	311 (12.9)	2371 (30.6)	9 (32.1)	134,329 (10.2)
Other ethnicities	209 (8.7)	996 (12.8)	0 (0)	556,855 (42.4)
>18 y	2401 (99.6)	6749 (86.95)	28 (100)	1,129,992 (85.9)
<18 y	9 (0.4)	1013 (13.05)	0 (0)	184,932 (14.1)

MS, multiple Sclerosis; Pas, periapical abscesses.

The different diagnoses were coded using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) international coding system. The patient population analyzed was mixed, presenting with different disease conditions including acute PAs without sinus. Individual data were not analyzed; however, all cases were diagnosed by 3 calibrated experienced dentists in a hospital setting for patients admitted to urgent care with symptoms of acute PAs. The calibrated dentists followed a strict diagnosis protocol of the emergency clinic.

A diagnosis was made based on clinical examination and imaging data confirming the diagnoses of acute PAs without a sinus tract. The inclusion criteria encompassed all patients with the corresponding diagnostic code for acute PAs without sinus (*ICD-10* code K04.7) and MS (*ICD-10* code G35). There were no exclusion criteria because all codes were computerized, and specific diagnoses of acute PAs in the total hospital patient population were searched using the appropriate *ICD-10* code. A history of MS was retrieved by searching the appropriate query in the database. A diagnosis of MS was made by the patient's physician.

Patients with an *ICD-10* diagnosis code of acute PAs were recorded, and the prevalence of acute PAs in patients with MS was compared with the prevalence in the total hospital patient population. In addition, an adjustment for diabetes mellitus (DM) and cardiovascular disease (CV) comorbidities was performed by querying the corresponding diagnosis codes (*ICD-10* codes E08–E013 and *ICD-10* codes I00–I99, respectively).

Logistic regression was conducted using the aggregated counts as weight in the model. Limited by i2b2 data, adjustment for DM and CV comorbidities was done for 1 covariate at a time. The SAS 9.4 (SAS Institute, Cary, NC) Logistic procedure was used to perform the statistical analysis.

Additionally, the odds ratio (OR) for the prevalence of acute PAs and its association with a history of EBV infection (*ICD-10* code B27.9) in the hospital patient population was calculated and analyzed.

RESULTS

The demographics of the hospital patient population studied is summarized in Table 1. The total hospital patient population studied was 1,314,924; 46.2% were males, and 53.8% were females (Table 1). Of the total hospital patient population, 0.18% were diagnosed with a history of MS. Females were more affected than males 3.25-fold. Whites were more affected than African Americans 6-fold. Whites were more affected than African Americans combined with other ethnicities 3.6-fold. Patients older than 18 years were affected almost exclusively. They were more affected than patients younger than 18 years more than 266-fold (Table 1).

TABLE 2 - Logistic Regression Result for Multiple Sclerosis (MS) and Periapical Abscesses (PAs)

Response: MS		Coefficient (OR)	2.50%	97.50%	P value
Intercept		1.40E-03	1.34E-03	1.46E-03	.0000
PAs	Yes vs no	2.2	1.44	3.23	.0001

OR, odds ratio.

TABLE 3 - Logistic Regression Result for Multiple Sclerosis (MS) and Periapical Abscesses (PAs) Adjusted for Diabetes Mellitus (DM) Comorbidity

Response: MS		Coefficient (OR)	2.50%	97.50%	*P* value
Intercept		1.27E-03	1.22E-03	1.33E-03	.0000
PAs	Yes vs no	2.6	1.38	2.93	.0002
DM	Yes vs no	3.17	2.81	3.55	.0000

OR, odds ratio.

TABLE 5 - Prevalence of Acute Periapical Abscesses (PAs) in Patients with a History of Epstein-Barr Virus (EBV) Infection

	PAs	Total patients
EBV, *n* (%)	15 (0.2)	639 (0.05)
Hospital	7762	1,314,924
OR	3.98	
95% CI	2.3821–6.6386	
P value	<.0001	

CI, confidence interval; OR, odds ratio.

Of the total hospital patient population, 7762 patients (0.59%) were associated with acute PAs (Table 1). Females were more affected than males, and whites were more affected proportionally than African Americans (Table 1).

The OR for acute PAs in patients with a history of MS was 2.2, and the difference in prevalence compared with the total hospital patient population was statistically significant ($P < .0001$) (Table 2). After adjustment for DM comorbidity, the OR for acute PAs in patients with a history of MS was 2.6 (Table 3). After adjustment for CV comorbidity, the OR for PAs in patients with a history of MS was 1.27 (Table 4).

Of the total hospital patient population, 0.05% were diagnosed with a history of EBV infection (Table 5). Of the patients who presented with acute PAs, 0.2% were diagnosed with a history of EBV infection (Table 5). The OR was 3.98, and the difference in prevalence was statistically significant ($P < .0001$) (Table 5).

DISCUSSION

The results of this hospital-based study show that overall the OR for the prevalence of acute PAs is significantly higher in patients with MS than in patients without this condition. Although the prevalence of acute PAs in the general hospital population was relatively low, the prevalence of acute PAs in patients with MS was more than 2-fold higher than in non-MS patients.

It has been reported that comorbidities such as DM and CV may be associated with an increased prevalence for periapical disease[32–34]. The results of our study show that even after adjusting for DM comorbidity, the OR for the prevalence of acute PAs in patients with MS was still higher than that of the general hospital population. However, the OR was significantly reduced and became nonsignificant after adjusting for CV diseases, suggesting that this comorbidity plays an important role in the MS PA association.

Patients with MS often suffer from changes in bone metabolism that can lead to osteoporosis and osteopenia[35–37]. Osteoporosis may affect up to 30% of patients with MS, and osteopenia may affect more than 70% of such patients. A cross-sectional hospital-based study reported that the prevalence of acute PAs was significantly higher in patients with osteoporosis than in patients without osteoporosis[38]. Patients with osteoporosis are more prone to pathologic changes in the jaw bones[39]. Therefore, it is plausible that osteoporosis resulting from MS can further expose affected MS patients to the risk of poorer bone quality, bone resorption, and bone infections.

Although multiple factors may be involved in affecting bone metabolism in patients with MS, it has been suggested that the induction of the tumor necrosis factor–related apoptosis-inducing ligand and interferon-beta may influence osteoclastogenesis in these patients[40].

A quintessential longitudinal analysis has strongly implicated MS, a chronic neurodegenerative disease, with previous infection with EBV. The frequency of MS was significantly higher in patients with a history of EBV infection[18]. The skeletal and bony effects of EBV have been recognized and documented[22–25]. Our finding showing an increased prevalence of PAs in EBV-infected patients may be significant and confirmatory to the EBV-MS association.

Studies showed an association between EBV infection and symptomatic apical periodontitis[41–43]. It was suggested that most teeth with necrotic pulp and periapical lesions harbored herpesviruses, including EBV, in the periapical tissues[41]. Sabeti et al[42], using reverse-transcription polymerase chain reaction, found evidence of EBV in periapical lesions and suggested that EBV activation participated in the pathogenesis of symptomatic periapical lesions. Furthermore, it has been theorized that EBV infection was capable of damaging tissue defenses *in situ*, thereby permitting overgrowth of pathogenic microorganisms and causing clinically acute symptomatic periapical lesions[42,43].

Several limiting factors should be taken into consideration. First, this is a retrospective cross-sectional study of charts and as such cannot necessarily indicate causality. Second, the study design does not allow for simultaneous multivariant analysis of all possible covariables. Third, socioeconomic reasons may influence the decision of certain patients when seeking a location for their medical and dental care. Therefore, the prevalence of acute PAs in this study may also reflect social-economic disparities. Nonetheless, the results of this study suggest an association between MS and acute PAs and that EBV may play a role.

TABLE 4 - Logistic Regression Result for Multiple Sclerosis (MS) and Periapical Abscesses (PAs) Adjusted for Cardiovascular (CV) Diseases Comorbidity

Response: MS		Coefficient (OR)	2.50%	97.50%	*P* value
Intercept		8.82E-04	8.34E-04	9.32E-04	<.0001
PAs	Yes vs no	1.27	0.83	1.86	.2438
CV	Yes vs no	4.62	4.27	5.01	<.0001

OR, odds ratio.

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