Candida species in patients with oral dysesthesia: a comparison of carriage among oral disease states.

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Abstract

Objectives

Oral dysesthesia (burning mouth syndrome) is characterised by a burning-like sensation of the oral mucosa. The aetiology of this disorder is still unknown, however associations with oral fungal carriage have been proposed and applied clinically. The aim of the this study was to compare oral *Candida* carriage in patients with oral dysesthesia with *Candida* carriage in patients with other commonly diagnosed oral diseases to clarify the relationship between *Candida* and oral dysesthesia.

Subjects and Methods

441 patients in total including 79 patients diagnosed with oral dysesthesia were included in this study. A retrospective analysis of mycological investigations undertaken in patients with clinically diagnosed oral dysesthesia compared with other oral conditions was undertaken.

Results

Oral carriage of *Candida* was found in 63.3% (50 of 79) of patients with oral dysesthesia. The frequency of carriage, and oral load of *Candida* were not significantly increased in patients with oral dysesthesia relative to the other conditions assessed. Patients with clinical signs of fungal infection or xerostomia presented with increased carriage of *Candida*.

Conclusion

There is no association between oral dysesthesia and the presence or load of oral *Candida*.

Introduction

Oral dysesthesia (OD), also known as Burning Mouth Syndrome (BMS), is a chronic orofacial pain condition that is associated with moderate to intense pain of a burning or similar nature, which affects the oral mucosa [1,2]. Patients affected by this condition may suffer disruption to normal social relationships and a general diminution in quality of life [3,4]. The International Association for the Study of Pain, International Headache Society and other recent literature have provided classification and diagnostic criteria for BMS that may be applied in both clinical and research settings (Table 1) [5-8].

BMS typically affects women more frequently than men at a female to male ratio of approximately 3:1 [2]. The majority of affected individuals are over 50 years of age and the post-menopausal period of life is frequently implicated [9,10]. The prevalence of BMS is estimated to be between 0.7% and 4.5% based on different sample populations and inclusion criteria [9-13]. The lack of strict protocols for clinical and serological examination of patients to differentiate between BMS and other diseases associated with painful intra-oral mucosal symptoms continues to hinder a sound epidemiological understanding of BMS being established from existing research [2,10].

The aetiopathogenesis of OD principally reflects psychological factors, and a number of systemic (e.g. diabetes mellitus) and local factors have all been suggested to be related to symptoms [2]. Infection by *Candida albicans* continues

to be quoted as a possible cause but there are no consistent supportive data [14-17]. As *Candida* is a commensal, it might be expected to frequently give rise to oral mucosal discomfort in patients at risk of candidal overgrowth, but not other conditions.

Reports of *Candida* oral carriage rates among BMS patients range from 25% to 93.7% within the published literature [14-16,18-23]. Three independent studies have shown no statistically significant difference in the rate of *Candida* carriage between BMS and control subjects [18,19,23]. A recent Japanese study found no significant difference between the oral carriage of *Candida* among BMS patients compared with xerostomia or dysgeusia [18]. Comparison of the *Candida* carriage of BMS patients relative to other oral diseases may yield further vital evidence to support or deny an association.

The aim of this research was to investigate the relationship between *Candida* and OD by examining the presentation, frequency and oral load of *Candida* in patients with a variety of oral diseases. The inclusion of a large cohort, assessment of a national population that has not been previously studied in this field, and comparison of a wide range of oral disease states are unique aspects of this study that are likely to provide a deeper understanding of the association between *Candida* and the presence of abnormal oral signs and symptoms.

Materials and Methods

The study constituted an audit of records for a convenience sample of 441 patients who had a variety of oral mucosal and non-mucosal diseases, including burning mouth syndrome, atypical facial pain, oral candidosis, angular stomatitis, *Candida*-associated denture induced stomatitis, geographic tongue, hyperplasia, oral epithelial dysplasia, oral squamous cell carcinoma, recurrent aphthous ulceration, xerostomia, oral lichen planus, pemphigus vulgaris and mucous membrane pemphigoid; the diagnoses being based upon clinical features alone. The study cohort included 277 females and 164 males. The mean age of patients participating in the study was 54.7 years, with a range extending from 4.4 to 88.7 years of age. Further details of demographics are provided in Table 2.

All patients were attendees of the Oral Medicine Clinic of the UCL Eastman Dental Hospital, London, United Kingdom. Patient consent was obtained for clinical oral examination, oral rinse collection and evaluation of yeast growth. All patients underwent microbiological estimation of oral *Candida* carriage as part of their standard of care routine clinical work up during a period of two years (between 1993-1995) when this diagnostic service was available to resident clinicians. Patients were required to swill 10 ml of sterile distilled water around the mouth for 60 seconds before expectorating into a sterile specimen container. 1 ml of this sample was cultured on Sabouraud's dextrose agar (Sigma-Aldrich, Poole, UK) containing chloramphenicol (1 mg/l; Sigma-Aldrich). Colony forming units (cfu) per ml of mouth swill were calculated.

Isolates were defined to the species level by phenotypic methods. A germ-tube test (GTT) [presence of germ tubes after growth in horse serum (Sigma-Aldrich) for 90 min at 37°C] gave a positive identification for *C. albicans* or *C. dubliniensis.*

The clinical and laboratory data were collated through a record audit to assess the comparative effects that different diseases may have on the presence of *Candida* species and the oral load of *Candida* within the oral cavity. Statistical analyses were performed with GraphPad Prism Version 4.01 (GraphPad Inc, San Diego, CA, USA). The Wilcoxon rank-sum test and Fisher's exact test were used to determine the difference in *Candida* load and presence respectively between different disease groups. A probability (p) of less than or equal to 0.05 was set as an indication of statistically significant variations.

Results

Frequency of oral carriage of Candida species

Oral carriage of *Candida* was found in 63.3% (50 of 79) of patients with OD. *Candida* species were found in 90.9% of individuals with xerostomia (20 of 22). Patients with clinical signs of *Candida* infection (denture induced stomatitis or candidosis/angular cheilitis) showed the presence of *Candida* species in 84.4% (38 of 45) and 83.9% (73 of 87) of cases respectively. A diagnosis of hyperplasia /dysplasia/squamous cell carcinoma was associated with *Candida* in 71.9% (41 of 57) of patients. Patients with mucocutaneous disease (oral lichen planus/pemphigus vulgaris/mucous membrane pemphigoid) and RAS presented

with *Candida* in 59.7% (43 of 72) and 56.3% (18 of 32) of patients. 57.1% (16 of 28) of patients with geographic tongue carried *Candida* species (Table 3).

Statistical analysis of the frequency of *Candida* carriage among the subgroups showed no significant differences ($P<0.05$) with exception of the subgroups of patients diagnosed with xerostomia, *Candida*-associated denture induced stomatitis and candidosis/angular cheilitis. The oral load of *Candida* species was significantly higher in these three groups relative to BMS patients.

Candida load

The mean count of *Candida* in individuals with BMS was 4,705 cfu (range from 0 – 52,000 cfu). The mean oral load of *Candida* among xerostomia patients was 9,175 (range from 0 – 45,300 cfu). Patients with clinical signs of *Candida* infection (denture induced stomatitis/*candidosis*/angular cheilitis) showed the mean count of *Candida* to be 8,920 (range from 0 – 67,000 cfu) and 8,197 (range from 0 – 121,000 cfu) respectively. A diagnosis of hyperplasia/dysplasia/squamous cell carcinoma was associated with a mean *Candida* count of 3,448 (range from 0 – 45,000 cfu). Mucocutaneous disease (oral lichen planus/pemphigus vulgaris/mucous membrane pemphigoid) and RAS were associated with the mean *Candida* count of 2,506 (range from 0 – 40,000 cfu) and 1,216 (range from 0 – 10,000 cfu).

Statistical analysis of the *Candida* counts among the subgroups showed no significant differences ($P<0.05$) with the exception of the subgroups of patients

diagnosed with xerostomia, denture induced stomatitis and candidosis/angular cheilitis. The oral load of *Candida* species was significantly higher in these three groups when compared with the BMS patient group (Table 3).

Discussion

The results of this paper support the hypothesis that there is no association between the presence or load of *Candida* and the diagnosis of burning mouth syndrome/oral dysesthesia. This assertion is made on the basis that *Candida* carriage was not found to be significantly higher among patients with BMS than the other oral diseases assessed.

The frequency of carriage of *Candida* species in the present group of patients was 63.3%. Previous studies have reported that 25% to 93.7% of patients with BMS may carry *Candida* [14-16,18-23], however it is critical to note that most show that the frequency of carriage among BMS patients is not significantly greater than in control groups [18,19,23]. Indeed, 70% or more of healthy patients may harbor *Candida* species in the mouth [24].

BMS patients within this study did not exhibit a significantly higher prevalence or load of *Candida* than any other oral disease examined. The oral carriage of *Candida* among patients with BMS was in fact found to be significantly lower than in patients diagnosed with xerostomia, *Candida*-associated denture induced stomatitis and candidosis/angular cheilitis. The significantly higher carriage of *Candida* species observed in patients with clinical signs of *Candida* infection

(denture induced stomatitis, candidosis/angular cheilitis) or local predisposing factors for increased *Candida* carriage (xerostomia) would be anticipated [18]. This finding may be a reassuring indication that the absence of association between *Candida* carriage and BMS demonstrated within the data presented is likely to be genuine. Further evidence of consistency is suggested by the general similarity in P-value among corresponding conditions when examining *Candida* count and prevalence using separate statistical analyses.

An interesting finding within this study is a very high mean level of *Candida* among patients with atypical facial pain. The authors do not believe that this is an indicative finding since high outliers in this group skewed the data. Indeed the median is considered more representative of the general distribution of load and was therefore used in tests for significant differences in *Candida* prevalence among different disease states.

As no detailed *Candida* typing was undertaken as part of this study, it is possible that some of the supposed *C. albicans* isolates may have been *C. dubliniensis*. It is likely however, that *C. albicans* was the most common type of *Candida* present, as previous studies of generally well individuals and those with BMS have consistently found *C. albicans* to be the dominant oral yeast [15,17,19,21,24].

The lack of a healthy control group for comparison within this study is a weakness that may be counteracted by a strong body of existing research that refutes the presence of a significant difference between *Candida* carriage among BMS versus control patients [18,19,23]. The data presented confirms previous findings that the existence of xerostomia is associated with increased *Candida* presence [18,21]. Since no previous research has compared *Candida* carriage among BMS patients with a wide range of alternative oral diseases, this unique perspective lends significant weight to the growing body of evidence that discredits a microbiological link between *Candida* infection and BMS.

Such a conclusion also yields important implications for the pharmaceutical management of BMS. Topical clonazepam therapy is currently the only effective pharmaceutical intervention for BMS that is based on a randomised controlled trial [6,25] and is well supported by other studies [26,27]. There is currently no sound research to support the use of antifungal medication in the management of correctly diagnosed BMS [6,20]. The findings of this study provide further evidence against a microbiological rationale for such an approach.

A secondary application of these findings may arise through assessment of the diagnostic potential for *Candida* testing to distinguish between different presenting oral diseases. The present results indicate that *Candida* testing may be useful to distinguish between BMS and frank oral candidosis or a

predisposing oral environment of xerostomia. However, the clinician must balance the information to be gained from this diagnostic procedure against considerations of costs, risks and delays in treatment that such a test may potentiate. Considering the differentiation potential that a simple clinical history, examination and in-chair saliva test may yield, a further probe to measure *Candida* carriage in such circumstances may be diagnostically superfluous, despite its potential.

The present results strongly support the notion that *Candida* is not a local factor associated with the aetiology of BMS. Since carriage of *Candida* among BMS patients appears to bear no significant difference to many other oral diseases, routine mycological evaluation of patients with likely features of this disorder is not warranted and there is no sound microbiological rationale for the use of antifungal therapy in the management of BMS.

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Table 1. Inclusion and exclusion criteria for diagnosis of BMS.

Inclusion criteria	Exclusion criteria
1) Symptoms of diffuse burning pain of the tongue and/or oral mucosa that may or may not be associated with subjective oral dryness and loss or alteration of taste or sensation. 2) Burning pain almost every day. 3) Examination revealing normal mucosa in the region of burning. 4) Absence of systemic disorders or laboratory alterations known to be associated with orofacial pain.	1) Presence of specific local etiologic evidence for the burning such as otherwise defined diseases of the oral mucosa or hyposalivation. 2) Presence of specific systemic etiological evidence for the burning such as diabetes or anaemia. 3) Regular use of medications known to be associated with oral burning and/or alteration of taste or sensation.

Table 2. Demographics of patients with burning mouth syndrome and other oral mucosal disorders.

Disease group	Age (years)					Gender			
	Mean	SD	Median	Min	Max	Female	Male	Total	Percentage
Burning mouth syndrome	***57.9***	***14.0***	***58.8***	***18.4***	***83.6***	***60***	***19***	***79***	**17.9%**
Atypical facial pain	55.1	18.9	59.1	15.5	80.2	14	5	19	4.3%
Oral candidosis/angular cheilitis	56.6	15.8	59.2	19.3	84.5	51	36	87	19.7%
Candida-associated denture induced stomatitis	60.3	14.3	63.0	25.3	82.4	28	17	45	10.2%
Geographic tongue	46.6	16.6	48.2	11.6	76.8	23	5	28	6.3%
Hyperplasia/dysplasia/squamous cell carcinoma	51.9	14.0	54.6	24.2	79.8	24	33	57	12.9%
Recurrent oral ulceration	34.0	14.5	30.4	4.4	74.8	25	7	32	7.2%
Xerostomia	58.4	14.3	56.5	35.5	85.9	14	8	22	4.9%
Oral lichen planus/pemphigus vulgaris/mucous membrane pemphigoid	53.3	13.8	53.5	17.3	87.4	38	34	72	16.3%
All	54.7	16.0	56.8	4.4	88.7	277	164	441	

Table 3. *Candida* counts and prevalence compared between burning mouth syndrome and other groups.

Disease group	*Candida* (count)							*Candida* (prevalence)					
	Mean	SD	Median	Min	Max	P-value		Absent	Present	Total	Percent Prevalence	P-value	
Burning mouth syndrome	***4,705.2***	***10,799.8***	***100***	***0***	***52,000***	***n/a***		***29***	***50***	***79***	***63.3%***	***n/a***	
Atypical facial pain	12,452.6	41,033.5	600	0	180,000	0.677		6	13	19	68.4%	0.793	
Oral candidosis/angular cheilitis	8,197.8	17,880.8	1,000	0	121,000	0.003	*	14	73	87	83.9%	0.003	**
Candida-associated denture induced stomatitis	8,920.2	15,737.2	2,000	0	67,000	0.013	*	7	38	45	84.4%	0.014	**
Geographic tongue	2,420.0	4,517.0	60	0	16,000	0.567		12	16	28	57.1%	0.361	
Hyperplasia/dysplasia/squamous cell carcinoma	3,448.9	7,413.1	400	0	45,000	0.293		16	41	57	71.9%	0.192	
Recurrent oral ulceration	1,216.3	2,621.7	10	0	10,000	0.492		14	18	32	56.3%	0.524	
Xerostomia	9,175.0	11,807.6	4,000	0	45,300	0.013	*	2	20	22	90.9%	0.017	**
Oral lichen planus/pemphigus vulgaris/mucous membrane pemphigoid	2,506.9	6,524.5	90	0	40,000	0.654		29	43	72	59.7%	0.738	
All	7,220.0	30,823.5	460	0	180,000			129	312	441	70.7%		

* significantly higher median count than BMS group (Wilcoxon rank-sum test)
** significantly higher prevalence than BMS group (Fisher's exact test)