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ScienceDirect
British Journal of Oral and Maxillofacial Surgery 48 (2010) 469–472
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Clinical study of tongue pain: Serum zinc, vitamin B12, folic acid, and copper concentrations, and systemic disease

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Accepted 5 August 2009
Available online 6 September 2009

Abstract

The aim of this retrospective study of patients with tongue pain who showed no improvement after initial treatment and examination was to find out if their lack of response correlated with serum concentrations of zinc, vitamin B12, folic acid, and copper, and if it was associated with coexisting systemic diseases. We studied 311 patients for whom we had data about serum concentrations of these elements, and recorded whether they had any systemic diseases and were taking medicines regularly. One patient (0.3%) had a copper concentration outside the reference range; 2 patients (0.6%) had folic acid concentrations outside the reference range. The corresponding number for vitamin B12 was 5 (2%), and for zinc 30 (10%). The systemic diseases with the highest rates were: hyperlipidaemia ($n = 53$, 17%), gastritis or gastric ulcer ($n = 51$, 16%), angina pectoris ($n = 39$, 13%), diabetes mellitus ($n = 31$, 10%), thyroid disease ($n = 31$, 10%), mild mental disorder ($n = 27$, 9%), hypertension ($n = 18$, 6%), cerebral infarction ($n = 17$, 6%), leiomyoma ($n = 15$, 5%) and anaemia ($n = 15$, 5%).

Roughly 10% of the patients were deficient in zinc. This study suggested that the serum concentration of zinc was most important to the patients with tongue pain. Many patients had more than one systemic condition, and all were taking various drugs.

Keywords: Glossodynia; Serum zinc; Burning tongue

Introduction

Tongue pain is both complex and controversial because of its multifactorial aetiology.[1] The cause may be local (xerostomia, stomatitis, candidiasis, tooth disease, or periodontitis), systemic (pernicious anaemia, iron-deficiency anaemia, pellagra, arteriosclerosis, or diabetic neuropathy), or psychological (hypochondriasis, depression, or cancerphobia).

Many studies have emphasised the involvement of psychological factors, but the mechanisms of pain when there are no macroscopic abnormalities on the tongue are not known,[2] though it is usually easy to treat patients who have macroscopic abnormalities (atrophy, erosion, or ulcer).

The treatment becomes more complex when the symptoms do not improve after initial treatment (adjustment of a prothesis, or treatment of dental caries, stomatitis and tartar) and first-line examinations (microbiological examination for *Candida*, and haematological assessments of red blood cell count, packed cell volume, and haemoglobin concentration). The relation between the incidence and treatment of dysgeusia in patients with glossodynia and serum concentrations of zinc, copper and other substances have been reported.[3–5]

The aim of this retrospective study was to assess the part played by the serum concentrations of zinc, vitamin B12,

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0266-4356/$ – see front matter
doi:10.1016/j.bjoms.2009.08.001

folic acid and copper in the patients with tongue pain who did not improve after initial treatment and examination. We also considered the effect of systemic disease.

Patients and methods

This study took place at the First Department of Oral and Maxillofacial Surgery, Osaka Dental University and Department of Oral and Maxillofacial Surgery, Fukui Prefectural Hospital, Japan, between April 1999 and December 2003 among patients whose chief complaint was tongue pain.

Before treatment was started, all patients were interviewed and examined extraorally and intraorally. Next, we adjusted prostheses; treated dental caries or tartar, or both; and prescribed gargle or ointment, or both; as necessary. We also took microbiological swabs to rule out intraoral candidiasis, and took blood for measurement of counts of white cells, red cells, packed cell volume, and platelets; concentrations of haemoglobin, total bilirubin, cholesterol, urea, creatinine and glucose; and activities of asparatate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, γ-glutamyl transpeptidase, and amylase.

All patients were assessed clinically by an oral and maxillofacial surgeon, whose selection of patients for this retrospective study was based on the following exclusion criteria: age younger than 18 years; idiopathic erosion, or ulcer of oral mucosa, or both; trauma as a result of dental caries, prostheses, or tartar; having current orthodontic treatment; presence of severe periodontal disease; confirmed candidiasis; previous treatment for glossalgia; previous or present medication with zinc, vitamin B12, folic acid and copper; history of drug abuse; and severe psychosis with speech disorder (dementia or schizophrenia).

A total of 311 patients (77 men and 234 women; mean age 66 years, range 21–89) was selected for this retrospective study. Patients gave informed consent to all the tests. Serum zinc concentration was measured by the atomic absorption spectrophotometer Model 153 (Instrumentation Laboratory, Inc., Lexington, MA, 02137; reference range 65–110 pg/ml). Vitamin B12 was measured with the Automated Chemiluminescence System (reference range; 180–941 pg/ml). Folic acid was measured with the Chemilumianalyzer ACS-180 or the Automated Chemiluminescence System (reference range; 3.6–12.9 ng/ml). Copper was measured with the colorimetric method and the Automated Analyzer HITACHI 7170. All blood was taken in the mornings (reference range; 68–128 μg/dl).

Results

Age distribution and male:female ratio are shown in Table 1.

Results of serum concentrations of zinc, vitamin B12, folic acid, and copper are shown in Table 2.

Table 1
Age and sex distribution of patients with tongue pain. Data are number (%).

Age (years)	Male	Female	Total
0–10	–	–	–
11–20	–	–	–
21–30	1	4	5 (2)
31–40	3	5	8 (3)
41–50	7	17	24 (8)
51–60	10	41	51 (16)
61–70	16	62	78 (25)
71–80	29	76	105 (34)
81–90	11	29	40 (13)
Total	77	234	311 (100)

Table 2
The rate of abnormal measurements for each substance examined. Data are number (%).

Age (years)	Zinc	Vitamin B12	Folic acid	Copper
0–10	–	–	–	–
11–20	–	–	–	–
21–30	–	–	–	–
31–40	–	–	–	–
41–50	3	1	–	–
51–60	3	–	–	–
61–70	8	–	–	1
71–80	8	3	2	–
81–90	8	1	–	–
Total	30/311 (10)	5/311 (2)	2/311 (0.6)	1/311 (0.3)

Previous or present systemic diseases are shown in Table 3.

Discussion

The mechanisms of tongue pain when there are no macroscopic abnormalities are not known. In general, these cases are often described as glossodynia, which is also known as glossalgia, glossopyrosis, stomatodynia, or burning mouth syndrome. It is characterised by a burning sensation in the tongue, often in the absence of clinical and laboratory findings.[6]

However, the definition and criteria of glossodynia is ambiguous. Nagai et al. defined it as “superficial and sponta-

Table 3
The rates of systemic disease among patients. Data are number (%).

Disease	Male	Female	Total
Hyperlipidaemia	3	50	53 (17)
Gastritis or gastric ulcer	5	46	51 (16)
Angina pectoris	23	16	39 (13)
Diabetes mellitus	9	22	31 (10)
Thyroid disorder	0	31	31 (10)
Mild mental disorder	8	19	27 (9)
Hypertension	5	13	18 (6)
Brain infarction	2	15	17 (6)
Leiomyoma	0	15	15 (5)
Anaemia	1	14	15 (5)
Asthma	2	9	11 (4)
Hepatitis C	3	8	11 (4)

neous pain or abnormal sensation on the tongue" and noted that glossodynia differs from neuralgia and does not involve organic changes on the tongue.[7] Sensations that have been described with glossodynia include burning in the mouth and tingling on the tongue. The incidence of glossodynia is high, and it is second only to dysgeusia among gustatory disturbances.

However, Osaki et al. reported that candidiasis may induce pain in the tongue without objective signs.[8] Terai et al. also reported that an atrophic tongue was associated with pain on eating, even if the atrophic change was slight, and this was likely to have been induced by *Candida*.[9]

It is usually easy to diagnose oral candidiasis because it has a white pseudomembrane. However, there are many cases of invisible oral candidiasis, and we excluded it by microbiological testing.

Most of our patients with tongue pain were old women, which suggested to us a menopausal cause. The age distribution of the patients who were outside the reference ranges for serum zinc, vitamin B12, folic acid, and copper concentrations were similar and almost equal to those for age distribution among the patients with tongue pain.

Many reports have stated that vitamin B12, iron, folic acid, and other substances are also associated with abnormal oral senses, in particular the oral signs of glossitis and stomatitis have long been associated with vitamin B12 and iron deficiency.[10–12] These oral changes may occur in the absence of anaemia or macrocytosis. Our total number of cases outside the normal range for vitamin B12 in serum was only 5 (2%). It is easy to diagnose vitamin B12 and iron deficiency by ordinary blood tests. Some patients had previously been taking, or were taking, vitamin B12 supplements. They were excluded from the selection criteria, so we gathered that the total number of patients with vitamin B12 deficiency was low. None were taking supplements for folic acid or copper.

A severe deficiency of zinc has been reported in patients with acrodermatitis enteropathica (a genetic disorder), after total parenteral nutrition without zinc, after excessive use of alcohol, and after treatment with penicillamine. The signs of severe zinc deficiency in humans include bullous pustular dermatitis, alopecia, diarrhoea, emotional disorder, weight loss, intercurrent infections as a result of cell-mediated immune dysfunction, hypogonadism, neurosensory disorders, and problems with healing of ulcers. If this condition is unrecognised and untreated, it is fatal.[13]

The signs of moderate deficiency of zinc include growth retardation and male hypogonadism in adolescents, rough skin, poor appetite, mental lethargy, delayed wound healing, cell-mediated immune dysfunction, and abnormal neurosensory changes.[13] It can also cause organic changes such as atrophy and flattening in the lingual papillae and that these can lead to dysgeusia.[5]

Tanaka et al. reported that in treating glossodynia it is important to diagnose the cause of pain and to give higher priority to treating that cause. The clinical efficacy of treatment will be improved when the presence or absence of dysgeusia is diagnosed early in the course of treatment.[2] In this study, the total number of cases outside the reference range for zinc in serum was 30 (10%). We also followed the course of the symptoms (tongue pain and dysgeusia) and treatment with zinc. Fifteen of 30 patients complained of both tongue pain and dysgeusia. In 27/30 patients the tongue pain was improved and in all 15 patients the dysgeusia was improved by treatment with zinc. All patients felt the improvement within 2–4 weeks of their treatment with zinc. It recurred in several patients 2–6 months after the treatment had finished.

Interpretation of zinc deficiency is known to be difficult. The lower limit of the reference range is highly susceptible to the influence of age, sex, time of day, oral contraceptive use and pregnancy, fasting, and general health. So it might be that there were many borderline cases of zinc deficiency.

In the near future, it will be necessary to make a more detailed study of the relation between taking zinc medication (term and dose), tongue pain (degree and area), and results of blood tests.

It has been reported that one of the aetiological diagnoses should be diabetes mellitus.[14] In the present study, several systemic diseases were implicated, including diabetes mellitus. Many patients had several systemic diseases and were taking different kinds of medicines. Many drugs (including tranquillisers and H2-blockers, among others) have thirst as a side effect. Drug-induced xerostomia is reported to be a cause of glossodynia.[15] These results suggest that glossodynia has a complex relation with systemic disease and habitual medicine. Prasad[13] also reported that an important relation existed between zinc deficiency and many systemic symptoms.

In conclusion, roughly 10% of patients were deficient in zinc. It was important to measure the serum concentration of zinc. A more detailed study is required of the relation between zinc and tongue pain.

Many patients had a number of systemic diseases and were taking several kinds of medicine. More detailed investigation of systemic disease and habitual drug-taking is also needed.

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