

RESEARCH ARTICLE

Open Access



# Oral manifestations in vitamin B<sub>12</sub> deficiency patients with or without history of gastrectomy

Jihoon Kim<sup>1</sup>, Moon-Jong Kim<sup>1</sup> and Hong-Seop Kho<sup>1,2\*</sup>

## Abstract

**Background:** The purpose of this study was to compare clinical features of vitamin B<sub>12</sub> deficiency patients with a history of gastrectomy to those without a history of gastrectomy.

**Methods:** Twenty-two patients with vitamin B<sub>12</sub> deficiency were included. Patients' chief complaints, oral manifestations, blood examination results, and past medical histories were reviewed.

**Results:** Eleven patients had a history of gastrectomy and 11 did not. The chief complaint was glossodynia in all patients. No significant differences were observed between the two groups regarding age, sex, symptom duration, or plasma vitamin B<sub>12</sub> level. Erythema and depapillation of the tongue were the most common findings, however less common among patients without a history of gastrectomy. Two patients with a history of gastrectomy and 5 patients without a history of gastrectomy had normal oral mucosa. Patients with a history of gastrectomy were more anemic. Oral symptoms of the majority of patients responded to antifungals and vitamin B<sub>12</sub> replacement. The suggested etiologies for vitamin B<sub>12</sub> deficiency in the patients without a history of gastrectomy were gastritis, medications, diet, autoimmunity, and early gastric cancer.

**Conclusions:** Vitamin B<sub>12</sub> deficiency and its associated etiological factors should be considered in patients with glossodynia, even those whose oral mucosa appears normal and who lack a history of gastrectomy.

**Keywords:** Oral, Vitamin B<sub>12</sub>, Gastrectomy

## Background

Glossodynia is one of the most common oral symptoms in elderly people. This symptom has various etiologies, including trauma, local infection, anemia, diabetes mellitus, nutritional deficiencies, and trigeminal neuropathy [1–3].

Vitamin B<sub>12</sub> is one of important nutritional components that affect oral health. Individuals with decreased levels of vitamin B<sub>12</sub> have been reported to exhibit various oral manifestations such as glossitis, glossodynia, recurrent ulcers, cheilitis, dysgeusia, lingual paresthesia, burning sensations, and pruritus [4–8]. Moreover, 64.3 % of vitamin B<sub>12</sub> deficiency patients (9 of 14 patients) with oral signs and symptoms were non-

anemic and normocytic, suggesting the importance of more detailed blood screening in this patient group [9].

Most patients with vitamin B<sub>12</sub> deficiency encountered in dental clinics have a history of gastrectomy due to gastric cancer. These patients have difficulty in absorbing vitamin B<sub>12</sub> because the source of intrinsic factor, a glycoprotein known to be involved in vitamin B<sub>12</sub> absorption in the ileum, is partly or totally eliminated by gastrectomy [10, 11]. However, vitamin B<sub>12</sub> deficiency has also been observed in elderly patients who have never undergone gastrectomy. It has been reported that certain diseases such as pernicious anemia [12, 13], gastritis [6, 14, 15] and thyroid diseases [16, 17], or some medications [18–21] are related to the absorption process of vitamin B<sub>12</sub>. In patients without a history of gastrectomy, oral manifestations of vitamin B<sub>12</sub> deficiency could be affected by the related medical conditions and/or medications. Therefore, this difference in

\* Correspondence: hkho@snu.ac.kr

<sup>1</sup>Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University, Yonkeun-Dong 28, Chongro-Ku, Seoul 110-749, Republic of Korea

<sup>2</sup>Institute on Aging, Seoul National University, Gwanak-Ro 1, Gwanak-Gu, Seoul 151-742, Republic of Korea



etiological factors could result in variations in oral changes according to the presence or absence of a gastrectomy history. However, there have been no reports which compare oral symptoms of vitamin B<sub>12</sub> deficiency patients with a history of gastrectomy with those without a history of gastrectomy.

In this study, we compared the clinical features of patients with vitamin B<sub>12</sub> deficiency according to the presence or absence of a gastrectomy history. Probable etiologies of vitamin B<sub>12</sub> deficiency in patients without a history of gastrectomy were also suggested.

## Methods

### Subjects

This study was a retrospective study based on chart review. Inclusion criteria was low vitamin B<sub>12</sub> level (<200 pg/mL) and there was no specific exclusion criteria. Among the patients who were examined and treated by one doctor (HSK) in the Department of Oral Medicine at Seoul National University Dental Hospital (SNUDH) from January 2006 to January 2015, 22 patients were found to have a decreased level of vitamin B<sub>12</sub> and were included in this study.

### Ethics

This chart review study was approved by the Institutional Review Board (IRB) of SNUDH (#CRI15013). The IRB authorized the exemption of informed consent from the subjects.

### Procedures

The oral symptoms, oral manifestations, blood examination results, and past medical history of each patient were reviewed. In addition, treatments, progression of oral symptoms, and medical consultation results were reviewed. Blood examinations were done during the initial evaluation before the commencement of treatments for oral symptoms. Among the results of blood examination, red blood cell (RBC) count (normal range: male,  $4.2\text{--}6.3 \times 10^6/\mu\text{L}$ ; female,  $4.0\text{--}5.4 \times 10^6/\mu\text{L}$ ), hemoglobin (Hb, normal range: male, 13–17 g/dL; female, 12–16 g/dL), hematocrit (Hct, normal range: male, 39–52 %;

female, 36–48 %), mean corpuscular volume (MCV, normal range: male, 81–96 fL; female, 79–95 fL), mean corpuscular hemoglobin (MCH, normal range: male, 27–33 pg; female, 26–32 pg), mean corpuscular hemoglobin concentration (MCHC, normal range: 32–36 g/dL), vitamin B<sub>12</sub> (normal range: 200–1000 pg/mL), folate (normal range: 3–15 ng/mL), and ferritin (normal range: 10–300 ng/mL) were included. When the result of vitamin B<sub>12</sub> level was '<25 pg/mL', the value of 25 pg/mL was used for the calculation of mean.

### Statistics

The significance of differences between the two groups was assessed by the Mann–Whitney U test (for continuous variables) and Fisher's exact test (for categorical variables). For each test, a *P* value less than 0.05 was considered statistically significant.

### Results

The demographic characteristics of the patients with vitamin B<sub>12</sub> deficiency are shown in Table 1. Of the total 22 patients, 11 had a history of gastrectomy (5 men and 6 women) and 11 did not (4 men and 7 women). Of 11 patients with a history of gastrectomy, 10 patients underwent gastrectomy due to gastric cancer and 1 patient due to abdominal rupture caused by a traffic accident. The two groups were not significantly different with respect to age (*P* = 0.323), duration of oral symptoms (*P* = 0.554), and vitamin B<sub>12</sub> level (*P* = 0.895).

The oral symptoms and findings from clinical examinations of the patients are shown in Table 2. The chief complaint was tongue pain for all patients. Other symptoms of the patients with a history of gastrectomy included dry mouth (6/11, 54.5 %) and pain in other intraoral mucosal areas (5/11, 45.5 %). The patients without a history of gastrectomy complained of pain in other intraoral mucosal areas (5/11, 45.5 %), dry mouth (3/11, 27.3 %), and dysgeusia (2/11, 18.2 %). Most of the patients from both groups were taking medications which could have been the cause for dry mouth. In the group with a history of gastrectomy, 1 patient was taking hypnotics and anti-parkinsonism drugs, 1 patient

**Table 1** Demographic characteristics of the patients with vitamin B<sub>12</sub> deficiency

	With a history of gastrectomy N = 11	Without a history of gastrectomy N = 11	<i>P</i> value
Sex (male/female)	5/6	4/7	1.000
Age (years) Mean ± SD (range)	62.6 ± 7.6 (51–73)	66.9 ± 9.9 (52–85)	0.323
Symptom duration (months) Mean ± SD (range)	64.5 ± 61.7 (1–180)	37.6 ± 31.9 (6–96)	0.554
Vitamin B <sub>12</sub> (pg/mL) Mean ± SD (range)	74.5 ± 51.2 (25–188)	64.2 ± 26.9 (25–123)	0.895

**Table 2** Oral symptoms and clinical findings in the patients with and without a history of gastrectomy

No	Age (years)	Sex	Chief complaint	Symptom duration (months)	Dry mouth	Pain in other oral mucosal areas	Dysgeusia	ET	DT	AC	FT	Other findings
With a history of gastrectomy												
1	68	F	Tongue pain	12	+	-	-	+	+	-	+	-
2	66	M	Tongue pain	1	-	+	-	+	+	-	+	erythema with erosion on the upper labial mucosa
3	59	F	Tongue pain	48	-	-	-	+	+	-	+	-
4	73	F	Tongue pain	14	+	-	-	+	+	-	+	-
5	53	M	Tongue pain	180	-	+	-	-	-	-	+	-
6	55	M	Tongue pain	60	-	+	-	-	-	-	-	whitish lesions with erythema and erosion on both buccal mucosa
7	51	F	Tongue pain	156	-	-	-	+	+	-	+	-
8	65	M	Tongue pain	12	+	-	-	+	+	-	-	-
9	57	F	Tongue pain	28	+	+	-	+	+	-	-	-
10	69	M	Tongue pain	54	+	+	-	+	+	+	+	-
11	73	F	Tongue pain	144	+	-	-	+	+	+	+	-
Without a history of gastrectomy												
1	63	F	Tongue pain	84	+	-	+	+	+	-	+	-
2	67	F	Tongue pain	72	-	-	-	+	+	-	-	-
3	73	F	Tongue pain	24	-	-	-	+	+	-	+	-
4	85	M	Tongue pain	12	-	+	-	-	-	-	+	-
5	56	F	Tongue pain	16	-	-	-	-	-	-	-	-
6	80	F	Tongue pain	6	+	-	-	-	-	-	+	-
7	60	F	Tongue pain	96	-	+	-	+	+	-	+	erythema on both buccal mucosa
8	70	F	Tongue pain	18	-	+	-	-	-	-	-	-
9	57	M	Tongue pain	18	-	+	-	+	+	-	+	-
10	73	M	Tongue pain	60	-	+	+	+	+	+	+	-
11	52	M	Tongue pain	8	+	-	-	-	-	-	+	-

ET, Erythema of the tongue; DT, Depapillation of the tongue; AC, Angular cheilitis; FT, Fissured tongue

had a history of chemotherapy, and 1 patient was taking hypnotics and had a history of chemotherapy. Such medications and treatment history might be related with the increased incidence of dry mouth in the gastrectomy group. Erythema and depapillation of the tongue were the most common findings (Figs. 1 and 2). Patients with erythema of the tongue also had depapillation of the tongue. The patients with a history of gastrectomy showed such oral manifestations more frequently compared with those without a history of gastrectomy. Erythema and depapillation of the tongue were observed in 9 (81.8 %) patients with a history of gastrectomy and 6 (54.5 %) patients without a history of gastrectomy ( $P=0.361$ ). Angular cheilitis was present in 2 patients with a history of gastrectomy and 1 patient without a history of gastrectomy. Fissured

tongue was observed in 8 patients of each group. Two patients (18.2 %) with a history of gastrectomy and 5 patients (45.5 %) without a history of gastrectomy had normal oral mucosa without erythema and depapillation of the tongue, or angular cheilitis ( $P=0.361$ ) (Figs. 3 and 4). Additionally, in the group with a history of gastrectomy, 1 patient showed erythema with erosion on the upper labial mucosa which seemed to be of a traumatic origin on the initial evaluation. The lesion was completely healed at the following appointment. Another patient showed whitish lichenoid lesions with erythema and erosion on both buccal mucosae. One patient without a history of gastrectomy showed erythema on both buccal mucosae which disappeared after anti-fungal therapy, suggesting the possibility of atrophic candidiasis.



**Fig. 1** Image of the tongue in a patient with a history of gastrectomy (No. 4). Erythema and depapillation of the tongue were observed

The blood examination results of the patients are shown in Table 3. Although there were no significant differences in the mean values of blood examination results between the two groups ( $P = 0.081 - 0.974$ ), it was notable that the patients with a history of gastrectomy tended to be more anemic. The RBC count was decreased in 8 patients (72.7 %) with a history of gastrectomy and 5 patients (45.5 %) without a history of gastrectomy ( $P = 0.387$ ). The Hb level was decreased in 8 patients (72.7 %) with a history of gastrectomy and 3 patients (27.3 %) without a history of gastrectomy ( $P = 0.086$ ). The Hct level was decreased in 7 patients (63.6 %) with a history of gastrectomy and 4 patients (36.4 %) without a history of gastrectomy ( $P = 0.395$ ).

The MCV was increased in 6 patients (54.5 %) in each group.

For management of oral symptoms, topical antifungal therapies were administered to 9 patients with a history of gastrectomy. These therapies included nystatin suspension (4 mL of 100,000 units/mL, 3 times/day, topical) for 5 patients, nystatin suspension with clonazepam (0.5 mg/day, topical) for 1 patient, fluconazole suspension (2.5 mL of 10 mg/mL, 2 times/day, topical) for 1 patient, fluconazole suspension with clonazepam (0.5 mg/day, topical) for 1 patient, and both nystatin and itraconazole suspensions (5 mL of 10 mg/mL, 2 times/day, topical) for 1 patient.



**Fig. 2** Image of the tongue in a patient without a history of gastrectomy (No. 3). Erythema and depapillation of the tongue were observed



**Fig. 3** Image of the tongue in a patient with a history of gastrectomy (No. 5). He had suffered from tongue pain for 15 years, but no pathologic signs were observed on the tongue, except for tongue fissures

One patient was prescribed carboxymethylcellulose (CMC)-based artificial saliva only, and 1 patient was referred to a physician at the first visit. Of the 9 patients who received topical antifungal therapy, 8 showed symptom improvement. All patients with a history of gastrectomy were referred to physicians for further evaluation and management. The results of only 9 patients were available, because 2 patients did not visit after the referrals. Intramuscular injection of vitamin B<sub>12</sub> was performed in 4 patients and the oral symptoms improved in all. Oral replacement therapy of vitamin B<sub>12</sub> was performed in 3 patients. The symptoms disappeared in 2 of these patients and partially improved in 1 of these patients. One patient

received both vitamin B<sub>12</sub> injection and oral folate replacement therapy; these treatments led to symptom improvement. One patient received oral vitamin B<sub>12</sub>, ferritin, folate replacement therapy, and vitamin B<sub>12</sub> injection and this therapy was effective.

Regarding the patients without a history of gastrectomy, topical antifungal therapy (nystatin suspension 4 mL of 100,000 units/mL, 3 times/day, topical) was administered to 6 patients, CMC-based artificial saliva and clonazepam (0.5 - 1.0 mg/day, topical and/or p.o.) to 4 patients, and CMC-based artificial saliva only to 1 patient. Of the 5 patients who did not undergo antifungal therapy, 4 patients did not have any pathologic oral



**Fig. 4** Image of the tongue in a patient without a history of gastrectomy (No. 4). No pathologic signs were observed on the tongue, except for tongue fissures and slight tongue coatings

**Table 3** Blood examination results of the patients with and without a history of gastrectomy

No	Age (years)	Sex	Symptom duration (months)	RBC ( $\times 10^6/\mu\text{L}$ )	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Vit. B <sub>12</sub> (pg/mL)	Folate (ng/mL)	Ferritin (ng/mL)
				M: 4.2-6.3	13-17	39-52	81-96	27-33	32-36	200-1000	3-15	10-300
				F: 4.0-5.4	12-16	36-48	79-95	26-32				
With a history of gastrectomy												
1	68	F	12	4.1	11.9	38.5	93.2	28.8	30.9	31.0	9.3	8.7
2	66	M	1	3.0	10.4	30.8	102.7	34.7	33.8	47.0	7.4	37.3
3	59	F	48	3.7	12.5	37.4	102.5	34.2	33.4	88.0	26.0	26.8
4	73	F	14	3.6	11.0	33.9	94.7	30.7	32.4	147.0	6.6	26.8
5	53	M	180	3.6	12.5	35.7	98.1	34.3	35.0	94.0	6.0	36.2
6	55	M	60	4.6	14.8	41.9	91.3	32.2	35.3	188.0	1.4	69.4
7	51	F	156	3.3	11.5	34.3	105.0	35.0	33.4	82.0	13.0	-
8	65	M	12	3.7	13.8	38.6	106.0	37.9	35.7	<25	14.1	30.2
9	57	F	28	3.6	8.9	29.8	84.0	25.2	30.0	68.0	17.5	3.0
10	69	M	54	2.6	11.4	34.3	130.0	43.1	33.2	25.0	75.0	264.6
11	73	F	144	4.2	11.8	36.7	86.9	28.1	32.3	<25	14.0	-
Mean	62.6		64.5	3.6	11.9	35.6	99.5	33.1	33.2	85.6	17.3	55.9
Without a history of gastrectomy												
1	63	F	84	3.9	12.0	35.9	93.0	31.0	33.4	<25	14.4	45.4
2	67	F	72	4.6	13.2	38.8	83.8	28.5	34.0	123.0	7.1	47.8
3	73	F	24	4.8	14.4	41.7	87.2	30.2	34.6	62.0	30.0	17.7
4	85	M	12	2.9	11.0	31.6	109.0	38.0	34.7	56.0	8.0	144.0
5	56	F	16	4.9	13.5	40.0	81.5	27.5	33.7	107.0	1.5	39.7
6	80	F	6	3.9	13.8	38.9	100.0	35.6	35.6	67.0	15.3	-
7	60	F	96	3.7	11.0	35.4	96.8	30.1	31.1	47.0	18.4	7.5
8	70	F	18	4.6	15.3	44.5	96.1	33.0	34.4	43.0	0.3	167.2
9	57	M	18	1.5	6.5	20.2	132.0	42.7	32.4	47.0	7.6	424.1
10	73	M	60	4.4	14.7	42.0	96.0	33.7	35.1	60.0	17.9	181.5
11	52	M	8	4.3	15.5	44.4	103.0	36.0	34.9	69.0	19.8	27.4
Mean	66.9		37.6	4.0	12.8	37.6	98.0	33.3	34.0	68.1	12.8	110.2

RBC, red blood cell count; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; Vit., vitamin

When the result of vitamin B<sub>12</sub> level was <25 pg/mL, the value of 25 pg/mL was used for the calculation of mean

No significant differences were found between the blood examination results of the patients with and without a history of gastrectomy (the Mann-Whitney U test,  $P > 0.05$ )

signs, with the exception of fissured tongue. All 6 patients who received topical antifungal therapy and all 4 patients who received CMC-based artificial saliva and clonazepam showed symptom improvement. The one patient who received CMC-based artificial saliva only did not show symptom improvement. Of the 11 patients in this group, 9 were referred to physicians for further evaluation and management. One patient refused the referral after exhibiting significant symptom improvement. The other patient could not be referred because the patient did not come to the clinic on the day that the

referral was scheduled. Of the 9 referred patients, 3 were treated with oral vitamin B<sub>12</sub> replacement therapy, 2 were given vitamin B<sub>12</sub> injection, and 2 were treated with both oral vitamin B<sub>12</sub> replacement and injection. All of them showed symptom improvement. One patient was treated with oral vitamin B<sub>12</sub> and iron replacement therapy; this treatment was effective. The other patient who underwent gastroscopy was diagnosed with early gastric cancer and underwent gastrectomy.

The probable etiologies of vitamin B<sub>12</sub> deficiency in the patients without a history of gastrectomy are shown

in Table 4. Five patients (No. 1, 3, 5, 6, and 8) suffered from gastritis, which might have caused the vitamin B<sub>12</sub> deficiencies in these patients. Three patients (No. 1, 2, and 4) had diabetes mellitus and were taking related medications, indicating that their diabetes medications were the probable etiologies. One of these patients (No. 1) was also taking thyroid hormone after thyroidectomy due to thyroid cancer. One patient (No. 7) was vegetarian; thus, insufficient intake of nutritional components containing vitamin B<sub>12</sub> might have caused the deficiency. An additional blood examination performed in the department of hematocology revealed that one patient (No. 9) had antibodies against the intrinsic factor. Another patient (No. 10) was diagnosed with early gastric cancer based on the result of a gastroscopy performed in the department of internal medicine. One patient (No. 11) underwent gastroscopy, which yielded normal results. No probable etiologic factors were reported in any of the medical histories or additional examinations done at the clinic to which the patient was referred.

Among 11 patients with a history of gastrectomy, 2 patients (No. 3 and 8) had gastritis, 2 patients (No. 4 and 11) had diabetes mellitus and were taking related medications, and 1 patient (No. 1) was taking thyroid hormone for hypothyroidism.

## Discussion

Our results showed that oral signs and symptoms and blood examination abnormalities were more common and also more severe in patients with a history of gastrectomy. Resection of the gastrointestinal tract was the definite cause although some of these patients had other medical conditions which might have played a role in

the pathogenesis of the vitamin B<sub>12</sub> deficiency. On the other hand, in patients without a history of gastrectomy, the severity and duration of diseases and/or the dose and duration of medication intake could have affected the clinical and laboratory results. Interestingly, 2 patients with a history of gastrectomy and 5 patients without a history of gastrectomy did not show any significant pathologic oral signs, except for tongue fissures. Decreased Hb and Hct levels were more common in patients with a history of gastrectomy compared to those without a history of gastrectomy. The probable etiologies for the vitamin B<sub>12</sub> deficiencies in the patients without a history of gastrectomy were gastritis, diabetes medications, a vegetarian diet, antibodies to the intrinsic factor, and early gastric cancer.

Atrophic gastritis, a very common disease with a high prevalence in elderly patients, has been known to be one of the most common causes of vitamin B<sub>12</sub> deficiency [6, 14, 15]. Chronic inflammation of the stomach wall causes atrophy of the gastric mucosa and decreased secretion of gastric acid, which can result in malabsorption of vitamin B<sub>12</sub>. Moreover, medications for gastritis, such as proton pump inhibitors, have been reported to inhibit gastric acid production, which might also cause malabsorption of vitamin B<sub>12</sub> [18, 20].

Metformin is one of the most commonly prescribed drugs for type 2 diabetes and is well known to be associated with vitamin B<sub>12</sub> deficiency [19, 21, 22]. Metformin inhibits gluconeogenesis, decreases hepatic glucose output, and increases insulin sensitivity. One of the most commonly reported side effects of metformin is gastrointestinal disorders, including reduced vitamin B<sub>12</sub> absorption. Metformin disturbs the metabolism of calcium which is one of the necessary elements for the body to absorb vitamin B<sub>12</sub> [22].

Although pernicious anemia is uncommon in Asians including Korean ethnicity [23, 24], this disease is another cause of vitamin B<sub>12</sub> deficiency [12, 13]. Pernicious anemia is an autoimmune disease characterized by the absence of intrinsic factor, a glycoprotein that is necessary for vitamin B<sub>12</sub> absorption [25, 26]. This condition prevents the normal absorption of vitamin B<sub>12</sub>, thereby resulting in vitamin B<sub>12</sub> deficiency. Vitamin B<sub>12</sub> is usually found in foods of animal origin, such as meat, poultry, fish, and eggs [7]. Therefore, a strict vegetarian diet could cause a vitamin B<sub>12</sub> deficiency, and vitamin B<sub>12</sub> replacement is recommended for vegetarians. Thyroid diseases have also been known to be associated with vitamin B<sub>12</sub> deficiency [16, 17]. Thyroid hormone stimulates erythropoiesis and anemia frequently develops in patients with thyroid hormone disorders. Megaloblastic anemia has been reported to be related to thyroid diseases, but this relationship is still controversial [27, 28].

The finding that 5 of 11 vitamin B<sub>12</sub> deficiency patients without a history of gastrectomy complained of

**Table 4** Probable etiologies in the patients without a history of gastrectomy

No	Age (years)	Sex	Symptom duration (months)	Probable etiology of vitamin B <sub>12</sub> deficiency
1	63	F	84	Medications for diabetes mellitus and Gastritis
2	67	F	72	Medications for diabetes mellitus
3	73	F	24	Gastritis
4	85	M	12	Medications for diabetes mellitus
5	56	F	16	Gastritis
6	80	F	6	Gastritis
7	60	F	96	Vegetarian diet
8	70	F	18	Gastritis
9	57	M	18	Antibodies to intrinsic factor
10	73	M	60	Early gastric cancer
11	52	M	8	Unknown

tongue pain in the absence of any significant pathologic oral signs suggests that blood examinations, including vitamin B<sub>12</sub> measurements, are mandatory for patients with glossodynia. Such examinations are important even for patients without a history of gastrectomy and for patients without any pathologic oral signs. Furthermore, the finding that 1 patient had early gastric cancer implies that gastroscopy is necessary for patients who have not undergone gastroscopy regularly.

Antifungal therapy was effective especially in patients with oral signs such as tongue erythema and depapillation, or angular cheilitis. Since vitamin B<sub>12</sub> deficiency can cause an anemic state in the body by attenuating the immune system, patients with vitamin B<sub>12</sub> deficiency are more susceptible to opportunistic infections such as candidiasis [29]. Some patients treated with clonazepam exhibited symptom improvement. Clonazepam is the preferred drug for treating burning mouth syndrome and has been widely used as a topical agent, an oral agent, and a combined way [30–33]. Vitamin B<sub>12</sub> deficiency has been reported to be related to peripheral neuropathy [7, 34]. Thus, some of the oral symptoms in our patients may be related to neuropathic changes of the trigeminal nerve.

As expected, vitamin B<sub>12</sub> replacement therapy was effective for most patients, regardless of their gastrectomy history. Interestingly, oral vitamin B<sub>12</sub> replacement therapy was also effective for the patients with a history of gastrectomy. Orally taken vitamin B<sub>12</sub> can be absorbed by an intrinsic factor-independent passive diffusion pathway. Oral vitamin B<sub>12</sub> replacement has been reported to be effective and safe treatment, even in patients with a history of total gastrectomy [10].

Our study showed that the most common oral symptom in patients with vitamin B<sub>12</sub> deficiency was tongue pain and the most common findings were erythema and depapillation of the tongue. These oral signs and symptoms and blood examination abnormalities were less common and also less severe in patients without a history of gastrectomy than those with a history of gastrectomy. Oral symptoms responded to antifungal therapy. Clonazepam could be of additional help. Vitamin B<sub>12</sub> replacement therapy was effective. Patients without a history of gastrectomy exhibited many probable etiologic factors, such as gastritis, medications for diabetes and/or gastritis, a vegetarian diet, autoimmunity, and gastric cancer.

## Conclusions

It is essential that complete medical histories including medication information should be obtained from all patients complaining of tongue pain, irrespective of their oral findings or gastrectomy history. Gastroscopy is strongly recommended for all patients with vitamin B<sub>12</sub> deficiency who do not have a history of gastrectomy.

## Abbreviations

CMC, carboxymethylcellulose; Hb, Hemoglobin; Hct, Hematocrit; MCV, mean corpuscular volume; RBC, red blood cell

## Funding

This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (No. 2013R1A1A2004910) and a National Research Foundation of Korea Grant, through the Oromaxillofacial Dysfunction Research Center for the Elderly (No. 2015048003) at Seoul National University in Korea.

## Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

## Authors' contributions

JK designed the study, wrote the protocol, collected clinical data, analyzed data, and wrote the initial draft of the paper. MJK also collected clinical data and analyzed data. HSK, who is acting as the corresponding author, designed the study, collected clinical data, analyzed data, and wrote the manuscript. All authors have critically discussed the results, revised the manuscript, and approved the final version.

## Competing interests

The authors declare that they have no competing interests.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

This chart review study was approved by the Institutional Review Board (IRB) of Seoul National University Dental Hospital (#CRI15013). The IRB authorized the exemption of informed consent from the subjects.

Received: 8 November 2015 Accepted: 18 May 2016

Published online: 27 May 2016

## References

- Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. *Crit Rev Oral Biol Med.* 2003;14:275–91.
- Lehman JS, Bruce AJ, Rogers RS. Atrophic glossitis from vitamin B12 deficiency: a case misdiagnosed as burning mouth disorder. *J Periodontol.* 2006;77:2090–2.
- Yoshida H, Tsuji K, Sakata T, Nakagawa A, Morita S. Clinical study of tongue pain: Serum zinc, vitamin B12, folic acid, and copper concentrations, and systemic disease. *Br J Oral Maxillofac Surg.* 2010;48:469–72.
- Graells J, Ojeda RM, Muniesa C, Gonzalez J, Saavedra J. Glossitis with linear lesions: an early sign of vitamin B12 deficiency. *J Am Acad Dermatol.* 2009; 60:498–500.
- Pontes HA, Neto NC, Ferreira KB, Fonseca FP, Vallinoto GM, Pontes FS, Pinto Ddos S Jr. Oral manifestations of vitamin B12 deficiency: a case report. *J Can Dent Assoc.* 2009;75:533–7.
- Brescoll J, Daveluy S. A review of vitamin B12 in dermatology. *Am J Clin Dermatol.* 2015;16:27–33.
- Shipton MJ, Thachil J. Vitamin B12 deficiency - A 21st century perspective. *Clin Med.* 2015;15:145–50.
- Chang JY, Wang YP, Wu YC, Cheng SJ, Chen HM, Sun A. Blood profile of oral mucosal disease patients with both vitamin B12 and iron deficiencies. *J Formos Med Assoc.* 2015;114:532–8.
- Field EA, Speechley JA, Rugman FR, Varga E, Tyldesley WR. Oral signs and symptoms in patients with undiagnosed vitamin B12 deficiency. *J Oral Pathol Med.* 1995;24:468–70.
- Kim HI, Hyung WJ, Song KJ, Choi SH, Kim CB, Noh SH. Oral vitamin B12 replacement: an effective treatment for vitamin B12 deficiency after total gastrectomy in gastric cancer patients. *Ann Surg Oncol.* 2011;18:3711–7.
- Hu Y, Kim HI, Hyung WJ, Song KJ, Lee JH, Kim YM, Noh SH. Vitamin B12 deficiency after gastrectomy for gastric cancer: an analysis of clinical patterns and risk factors. *Ann Surg.* 2013;258:970–5.
- Sun A, Wang YP, Lin HP, Chia JS, Chiang CP. Do all the patients with gastric parietal cell antibodies have pernicious anemia? *Oral Dis.* 2013;19:381–6.



13. Sun A, Chang JY, Wang YP, Cheng SJ, Chen HM, Chiang CP. Do all the patients with vitamin B12 deficiency have pernicious anemia? *J Oral Pathol Med.* 2016;45:23-7.
14. Kaptan K, Beyan C, Ural AU, Cetin T, Avcu F, Gülşen M, Finci R, Yalçın A. *Helicobacter pylori*-is it a novel causative agent in vitamin B12 deficiency? *Arch Intern Med.* 2000;160:1349–53.
15. Avcu N, Avcu F, Beyan C, Ural AU, Kaptan K, Ozyurt M, Nevruz O, Yalçın A. The relationship between gastric-oral *Helicobacter pylori* and oral hygiene in patients with vitamin B12-deficiency anemia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;92:166–9.
16. Ness-Abramof R, Nabriski DA, Braverman LE, Shilo L, Weiss E, Reshef T, Shapiro MS, Shenkman L. Prevalence and evaluation of B12 deficiency in patients with autoimmune thyroid disease. *Am J Med Sci.* 2006;332:119–22.
17. Jabbar A, Yawar A, Waseem S, Islam N, Ul Haque N, Zuberi L, Khan A, Akhter J. Vitamin B12 deficiency common in primary hypothyroidism. *J Pak Med Assoc.* 2008;58:258–61.
18. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? *J Am Med Dir Assoc.* 2008;9:162–7.
19. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley Jr GP. Association of biochemical B<sub>12</sub> deficiency with metformin therapy and vitamin B<sub>12</sub> supplements: the National Health and Nutrition Examination Survey, 1999–2006. *Diabetes Care.* 2012;35:327–33.
20. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA.* 2013;310:2435–42.
21. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. *Intern Emerg Med.* 2015;10:93–102.
22. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. *Diabetes Res Clin Pract.* 2012;97:359–67.
23. Carmel R. Reassessment of the relative prevalences of antibodies to gastric parietal cell and to intrinsic factor in patients with pernicious anaemia: influence of patient age and race. *Clin Exp Immunol.* 1992;89:74–7.
24. Song IC, Lee HJ, Kim HJ, Bae SB, Lee KT, Yang YJ, Park SY, Cho DY, Kim NY, Cho IS, Jo DY. A multicenter retrospective analysis of the clinical features of pernicious anemia in a Korean population. *J Korean Med Sci.* 2013;28:200–4.
25. Bizzaro N, Antico A. Diagnosis and classification of pernicious anemia. *Autoimmun Rev.* 2014;13:565–8.
26. Osborne D, Sobczyńska-Malefora A. Autoimmune mechanisms in pernicious anaemia & thyroid disease. *Autoimmun Rev.* 2015;14:763–8.
27. Caplan RH, Davis K, Bengston B, Smith MJ. Serum folate and vitamin B12 levels in hypothyroid and hyperthyroid patients. *Arch Intern Med.* 1975;135:701–4.
28. Lippi G, Montagnana M, Targher G, Salvagno GL, Guidi GC. Prevalence of folic acid and vitamin B12 deficiencies in patients with thyroid disorders. *Am J Med Sci.* 2008;336:50–2.
29. Paillaud E, Merlier I, Dupeyron C, Scherman E, Poupon J, Bories PN. Oral candidiasis and nutritional deficiencies in elderly hospitalised patients. *Br J Nutr.* 2004;92:861–7.
30. Gremeau-Richard C, Woda A, Navez ML, Attal N, Bouhassira D, Gagnieu MC, Laluque JF, Picard P, Pionchon P, Tubert S. Topical clonazepam in stomatodynia: a randomized placebo-controlled study. *Pain.* 2004;108:51–7.
31. Amos K, Yeoh S, Farah CS. Combined topical and systemic clonazepam therapy for the management of burning mouth syndrome: a retrospective pilot study. *J Orofac Pain.* 2011;25:125–30.
32. Heckmann SM, Kirchner E, Grushka M, Wichmann MG, Hummel T. A double-blind study on clonazepam in patients with burning mouth syndrome. *Laryngoscope.* 2012;122:813–6.
33. Ko JY, Kim MJ, Lee SG, Kho HS. Outcome predictors affecting the efficacy of clonazepam therapy for the management of burning mouth syndrome (BMS). *Arch Gerontol Geriatr.* 2012;55:755–61.
34. Leishear K, Boudreau RM, Studenski SA, Ferrucci L, Rosano C, de Rekeneire N, Houston DK, Kritchevsky SB, Schwartz AV, Vinik AI, Hogervorst E, Yaffe K, Harris TB, Newman AB, Strotmeyer ES. Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults. *J Am Geriatr Soc.* 2012;60:1057–63.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

