Original Article

Anemia, hematinic deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody positivity in burning mouth syndrome patients with vitamin B12 deficiency

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KEYWORDS
Burning mouth syndrome; Gastric parietal cell antibody; Hyperhomocysteinemia; Pernicious anemia;

Abstract  Background/purpose: Our previous study found that 42 of 884 burning mouth syndrome (BMS) patients have vitamin B12 deficiency. This study assessed whether the vitamin B12-deficient BMS (B12D/BMS) patients had significantly higher frequencies of anemia, hematinic deficiencies, hyperhomocysteinemia, and serum gastric parietal cell antibody (GPCA) positivity than healthy control subjects and evaluated whether all B12D/BMS patients had pernicious anemia (PA).

Materials and methods: The blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 42 B12D/BMS patients and 442 healthy control subjects were measured and compared.

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Burning mouth syndrome patients with vitamin B12 deficiency

Introduction

Burning mouth syndrome (BMS) is characterized by the presence of burning sensation of the oral mucosa, but oral examination reveals none of clinically apparent oral mucosal alterations. BMS occurs more frequently in middle-aged and elderly women. Clinically, BMS can be classified into the primary and secondary forms. The primary BMS is essential or idiopathic, in which none of organic local/systemic causes can be identified, and peripheral and central neuropathies are the possible etiologies. The secondary BMS is caused by local, systemic, and/or psychological factors.1,2

Our previous study found that 42 (4.8%) of 884 BMS patients have vitamin B12 deficiency.3 The etiologies of vitamin B12 deficiency include inadequate intake, food-bound vitamin B12 malabsorption, the presence of gastric parietal cell antibody (GPCA) or intrinsic factor antibody or both in sera of patients, ileal malabsorption in patients with enteritis or ileal resection, biologic competition including bacterial overgrowth and tapeworm infestation, and defective transport such as transcobalamin II deficiency.4 The GPCA can destroy gastric parietal cells, resulting in lack of intrinsic factors and hypochlorhydria.4 Intrinsic factor deficiency may lead to malabsorption of vitamin B12 from terminal ileum and finally the vitamin B12 deficiency.4,5 Vitamin B12 and/or folic acid deficiencies may lead to macrocytic anemia or hyperhomocysteinemia in BMS patients.8–11 In addition, decreased gastric secretion of hydrochloric acid may cause iron malabsorption and subsequent iron deficiency.12–14 Thus, it is interesting to know whether BMS patients with vitamin B12 deficiency (so-called B12D/BMS patients in this study) are prone to have significantly higher frequencies of anemia, serum iron vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA, thyroglobulin antibody, and thyroid microsomal antibody positivity.8,15–57

In this study, 42 B12D/BMS patients were retrieved from our previous study.2 We tried to assess whether the 42 B12D/BMS patients had significantly higher frequencies of anemia, serum iron vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects and evaluated whether all B12D/BMS patients had pernicious anemia (PA).

Materials and methods

Subjects

This study consisted of 42 (11 men and 31 women, age range 20–81 years, mean age 56.7 ± 15.5 years) B12D/BMS patients selected from 884 BMS patients in our previous study.2 For two BMS patients, one age- (±2 years of each patient’s age) and sex-matched healthy control subject was selected. Thus, 442 age- and sex-matched healthy control subjects (106 men and 336 women, age range 18–90 years, mean 57.5 ± 13.5 years) were selected and included in this study.2 All the BMS patients and healthy control subjects were seen consecutively, diagnosed, and treated in the Department of Dentistry, National Taiwan University Hospital (NTUH) from July 2007 to July 2017. Patients were diagnosed as having BMS when they complained of burning sensation and other symptoms of the oral mucosa but no apparent clinical oral mucosal abnormality was found.2 The detailed including and excluding criteria for our BMS patients and healthy control subjects have been described previously.2 In addition, none of the BMS patients had taken any prescription medication for BMS at least 3 months before entering the study.

The blood samples were drawn from 42 B12D/BMS patients and 442 healthy control subjects for the
Comparisons of means of parameters between 42 B12D/BMS patients and 442 healthy control subjects by Student’s t-test. The differences in frequencies of patients with low, moderate, or high serum homocysteinemia, and serum GPCA positivity between 42 B12D/BMS patients and 442 healthy control subjects were compared by chi-square test. In addition, comparisons of frequencies of patients with low, moderate, or high serum levels of iron and folic acid between 26 anemic B12D/BMS patients and 16 non-anemic B12D/BMS patients were performed by chi-square or Fisher exact test, where appropriate. The result was considered to be significant if the P-value was less than 0.05.

**Results**

Comparisons of MCV and mean blood Hb and serum iron, vitamin B12, folic acid, and homocysteine levels between 42 B12D/BMS patients and 442 healthy control subjects are shown in Table 1. Because men usually had higher blood levels of Hb and iron than women, these two mean levels were calculated separately for men and women. We found significantly lower mean blood Hb (for men and women) and serum iron (for men and women) and vitamin B12 levels as well as significantly higher MCV and mean serum homocysteine level in 42 B12D/BMS patients than in 442 healthy control subjects (all P-values < 0.05, Table 1).

According to the World Health Organization (WHO) criteria, microcytosis of erythrocyte was defined as having MCV < 80 fl, macrocytosis of erythrocyte was defined as having MCV ≥ 100 fl, and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia. Furthermore, patients with the serum iron level < 60 μg/dL, the serum vitamin B12 level < 200 pg/mL, or the serum folic acid level < 4 ng/mL were defined as having iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the serum homocysteine level > 12.3 μM (which was the mean serum homocysteine level of healthy control subjects plus two standard deviations) were defined as having hyperhomocysteinemia. By the above-mentioned definitions, 7.1%, 52.4%, 61.9%, 26.2%, 100.0%, 0.0%, 83.3%, and 42.9% of 42 B12D/BMS patients were diagnosed as having microcytosis, macrocytosis, blood Hb and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and serum GPCA positivity, respectively. We found that 42 B12D/BMS patients had significantly higher frequencies of microcytosis, macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than 442 healthy control subjects (all P-values < 0.001, Table 2).

We also found that 26 (61.9%) of 42 B12D/BMS patients had anemia (defined as having an Hb concentration < 13 g/dL for men and < 12 g/dL for women). Of the 26 anemic B12D/BMS patients, 15 had PA (defined as having anemia, an MCV ≥ 100 fl, a serum vitamin B12 level < 200 pg/mL, and the presence of serum GPCA positivity), 5 had macrocytic anemia (defined as having anemia and an MCV > 100 fl) other than PA, and 4 had normocytic anemia (defined as having

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**Table 1** Comparisons of mean corpuscular volume (MCV) and mean blood hemoglobin (Hb) and serum iron, vitamin B12, folic acid, and homocysteine levels between 42 burning mouth syndrome (BMS) patients with vitamin B12 deficiency (B12D/BMS patients) and 442 healthy control subjects.

| Group                     | MCV (fl)          | Hb (g/dL)    | Iron (μg/dL) | Vitamin B12 (pg/mL) | Folic acid (μg/mL) | Homocysteine (μM) |
|---------------------------|-------------------|--------------|--------------|---------------------|--------------------|-------------------|
|                           | Men               | Women        | Men          | Women               |                    |                   |
| B12D/BMS patients (n = 42)| 96.7 ± 11.9       | 12.5 ± 1.1   | 12.5 ± 1.1   | 77.1 ± 20.8         | 84.6 ± 28.4        | 168.9 ± 31.4      |
| (n = 11)                  | (n = 31)          | (n = 31)     | (n = 11)     | (n = 11)            |                    |                   |
| P-value                   | <0.001            | <0.001       | <0.001       | 0.002               | 0.010              | <0.001            |
| Healthy control subjects  | 90.4 ± 3.6        | 15.1 ± 0.8   | 13.5 ± 0.7   | 105.2 ± 28.0        | 97.8 ± 27.2        | 694.2 ± 220.2     |
| (n = 442)                 | (n = 336)         | (n = 336)    | (n = 106)    | (n = 106)           | (n = 336)          |                   |

* Comparisons of means of parameters between 42 B12D/BMS patients and 442 healthy control subjects by Student’s t-test.
### Table 2
Comparisons of frequencies of microcytosis (mean corpuscular volume or MCV < 80 fL), macrocytosis (MCV ≥ 100 fL), blood hemoglobin (Hb) and serum iron, vitamin B12, and folic acid deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody (GPCA) positivity between 42 burning mouth syndrome (BMS) patients with vitamin B12 deficiency (B12D/BMS patients) and 442 healthy control subjects.

| Group                        | Patient number (%) | Microcytosis (MCV < 80 fL) | Macrocytosis (MCV ≥ 100 fL) | Hb deficiency (Men < 13 g/dL, women < 12 g/dL) | Iron deficiency (<60 μg/dL) | Vitamin B12 deficiency (<200 pg/mL) | Folic acid deficiency (<4 ng/mL) | Hyperhomocysteinemia (>12.3 μM) | GPCA positivity |
|------------------------------|--------------------|-----------------------------|------------------------------|-----------------------------------------------|-----------------------------|------------------------------------|----------------------------------|----------------------------------|-----------------|
| B12D/BMS patients (n = 42)   | 3 (7.1)            | 22 (52.4)                   | 26 (61.9)                    | 11 (26.2)                                     | 42 (100.0)                  | 0 (0.0)                            | 35 (83.3)                       | 18 (42.9)                       |
| Healthy control subjects (n = 442) | 0 (0.0)        | 0 (0.0)                     | 0 (0.0)                      | 0 (0.0)                                        | 0 (0.0)                     | 0 (0.0)                            | 11 (2.5)                        | 8 (1.8)                         |

*P*-value

- Comparisons of frequencies of parameters between 42 B12D/BMS patients and 442 healthy control subjects by chi-square test.

### Table 3
Anemia types, iron and folic acid deficiencies, hyperhomocysteinemia, and gastric parietal cell antibody (GPCA) positivity in 26 anemic burning mouth syndrome (BMS) patients with vitamin B12 deficiency (B12D/BMS patients).

| Anemia type                        | Patient number (%) | Mean corpuscular volume (fL) | Iron deficiency (<60 μg/dL) | Folic acid deficiency (<4 ng/mL) | Hyperhomocysteinemia (>12.3 μM) | GPCA positivity |
|------------------------------------|--------------------|-----------------------------|-----------------------------|----------------------------------|----------------------------------|-----------------|
| B12D/BMS patients (n = 42)         |                    |                             |                             |                                  |                                  |                 |
| Pernicious anemia                  | 15 (57.7)          | ≥100                        | 5 (33.3)                    | 0 (0)                            | 15 (100.0)                      | 15 (100.0)      |
| Other macrocytic anemia            | 5 (19.2)           | ≥100                        | 1 (20.0)                    | 0 (0)                            | 5 (100.0)                       | 0 (0)           |
| Normocytic anemia                  | 4 (15.4)           | 80.0–99.9                   | 2 (50.0)                    | 0 (0)                            | 4 (100.0)                       | 1 (25.0)        |
| Thalassemia trait-induced anemia   | 2 (7.7)            | <74                         | 1 (50.0)                    | 0 (0)                            | 2 (100.0)                       | 0 (0)           |
| Total                              | 26 (100.0)         | 9 (34.6)                    | 0 (0)                       | 26 (100.0)                       | 16 (61.5)                      |                 |
anemia and an MCV between 80.0 fl and 99.9 fl), two had thalassemia trait—induced anemia (Table 3).

Distribution of patients with low, moderate, or high serum levels of iron and folic acid in 26 anemic B12D/BMS patients and in 16 non-anemic B12D/BMS patients is shown in Table 4. There were no significant differences in frequencies of patients with low, moderate, or high serum levels of iron and folic acid between 26 anemic B12D/BMS patients and 16 non-anemic B12D/BMS patients (Table 4).

Discussion

The major finding of this study was that 42 B12D/BMS patients had significantly higher frequencies of macrocytosis (52.4%), blood Hb (61.9%) and serum iron (26.2%) and vitamin B12 (100.0%) deficiencies, hyperhomocysteinemia (83.3%), and serum GPCA positivity (42.9%) than 442 healthy control subjects (all P-values < 0.001). Our previous study demonstrated that 56 vitamin B12-deficient AG (B12D/AG) patients had significantly higher frequencies of macrocytosis (53.6%), blood Hb (64.3%) and serum iron (26.8%) and folic acid (3.6%) deficiencies, hyperhomocysteinemia (89.3%), and serum GPCA positivity (55.4%) than 532 healthy control subjects (all P-values < 0.005). Moreover, our previous study also found that 90 oral mucosal disease patients (including 34 with AG only, 21 with BMS only, 6 with Behcet’s disease patients; 38 in one (25%) of 4 vitamin B12-deficient AG patients; 23 in 3 (10.0%) of 30 B12D/BMS patients; and in 17 (18.9%) of 90 vitamin B12-deficient oral mucosal disease patients. PA is also discovered in 10 (100.0%) of 10 vitamin B12-deficient MBS patients; in 4 (12.5%) of 32 vitamin B12-deficient recurrent aphtous stomatitis patients; and in one (25%) of 4 vitamin B12-deficient Behcet’s disease patients; in 6 (24.0%) of 25 vitamin B12-deficient oral lichen planus patients; in 3 (23.1%) of 13 vitamin B12-deficient erosive oral lichen planus patients; and in 13 (48.1%) of 27 vitamin B12-deficient erosive oral lichen planus patients with desquamative gingivitis. These findings indicate that vitamin B12 deficiency results in macrocytosis and hyperhomocysteinemia in oral mucosal disease patients (including BMS and AG patients) with vitamin B12 deficiency.

B12D/BMS patients are supposed to have macrocytic anemia or PA, because severe vitamin B12 deficiency can lead to macrocytosis or PA. The present study found that 20 (47.6%) of 42 B12D/BMS patients have macrocytic anemia. Of these 20 B12D/BMS patients with macrocytic anemia, 15 had PA and 5 had macrocytic anemia other than PA. Our previous studies showed PA in 22 (39.3%) of 56 B12D/AG patients and in 17 (18.9%) of 90 vitamin B12-deficient oral mucosal disease patients. PA is also discovered in 10 (100.0%) of 10 vitamin B12-deficient MBS patients; in 4 (12.5%) of 32 vitamin B12-deficient recurrent aphtous stomatitis patients; in one (25%) of 4 vitamin B12-deficient Behcet’s disease patients; in 6 (24.0%) of 25 vitamin B12-deficient oral lichen planus patients; in 3 (23.1%) of 13 vitamin B12-deficient erosive oral lichen planus patients; and in 13 (48.1%) of 27 vitamin B12-deficient erosive oral lichen planus patients with desquamative gingivitis. These findings indicate that vitamin B12 deficiency results in macrocytosis and hyperhomocysteinemia in oral mucosal disease patients (including BMS and AG patients) with vitamin B12 deficiency.

Homocysteine is formed during methionine metabolism. Both vitamin B12 and folic acid act as coenzymes for the conversion of homocysteine to methionine. Moreover, vitamin B6 is a coenzyme for the conversion of homocysteine to cysteine. Therefore, patients with vitamin B12, folic acid, and/or vitamin B6 deficiencies may have hyperhomocysteinemia. This study demonstrated hyperhomocysteinemia in 35 (83.3%) of 42 B12D/BMS patients and folic acid deficiency in none (0%) of 35 hyperhomocysteinemia B12D/BMS patients. Our previous study also showed hyperhomocysteinemia in 30 (89.3%) of 56 B12D/AG patients and folic acid deficiency in 2 (4%) of 50 hyperhomocysteinemia B12D/AG patients. Moreover, hyperhomocysteinemia and folic acid deficiency are found in 65 (72.2%) and none (0%) of 90 vitamin B12-deficient oral mucosal disease patients, respectively. These findings suggest that vitamin B12 deficiency plays a major role in

| Table 4 Distribution of patients with low, moderate, or high serum levels of iron and folic acid in 26 anemic B12D/BMS patients and in 16 non-anemic B12D/BMS patients. |
|---|---|---|
| Group | Patient number (%) | P-value |
| --- | --- | --- |
| Anemic B12D/BMS patients (n = 26) | | |
| < 60 | 9 (34.6) | 2 (12.5) | 0.158 |
| Between 60 and 100 | 15 (57.7) | 9 (56.3) | 0.819 |
| ≥ 100 | 2 (7.7) | 5 (31.2) | 0.085 |
| Serum folic acid level (ng/mL) | | | |
| < 4 | 0 (0.0) | 0 (0.0) | NA |
| Between 4 and 15 | 13 (50.0) | 9 (56.3) | 0.940 |
| ≥ 15 | 13 (50.0) | 7 (43.7) | 0.940 |

NA = not assessed.

*Comparisons of frequencies of patients with low, moderate, or high serum levels of iron and folic acid between 26 B12D/BMS patients and 16 non-anemic B12D/BMS patients by chi-square or Fisher exact test, where appropriate.
causing hyperhomocysteinemia in 42 B12D/BMS patients, 56 B12D/AG patients, and 90 vitamin B12-deficient oral mucosal disease patients.

GPCA can induce destruction of gastric parietal cells, resulting in failure of intrinsic factor production and ileal malabsorption of vitamin B12 that finally leads to significantly higher frequencies of macrocytosis, anemia (including macrocytic, normocytic, and microcytic anemias), and vitamin B12 deficiency in our 42 B12D/BMS patients than in 442 healthy control subjects. However, the serum GPCA positivity was found in only 18 (42.9%) of our 42 B12D/BMS patients, in only 31 (55.4%) of our 56 B12D/AG patients, and in only 43 (47.8%) of 90 oral mucosal disease patients with vitamin B12 deficiency. For 24 B12D/BMS patients, 25 B12D/AG patients, and 47 vitamin B12-deficient oral mucosal disease patients without serum GPCA positivity, the vitamin B12 deficiency may be due to other factors such as inadequate intake, vitamin B12 malabsorption, biologic competition including bacterial overgrowth and tapeworm infestation, and transcobalamin II deficiency.

The serum iron deficiency was found in 11 (26.2%; 6 patients also had serum GPCA positivity) of 42 B12D/BMS patients. Our previous study discovered serum iron deficiency in 15 (26.8%; 12 patients also had serum GPCA positivity) of 56 B12D/AG patients. These findings indicate that the GPCA-induced reduction of gastric hydrochloric acid secretion may play a major role in causing serum iron deficiency in our 42 B12D/BMS and 56 B12D/AG patients, although other factors such as decreased absorption (due to gastrectomy, duodenal bypass, Helicobacter pylori infection, celiac sprue, inflammatory bowel diseases, etc.), chronic blood loss (peptic ulcer, diverticulitis, angiodysplasia, hook worm infestation, etc.), and drug-related (glucocorticoids, nonsteroidal anti-inflammatory drugs, proton-pump inhibitors, etc.) iron deficiency may also play roles in causing iron deficiency in our 42 B12D/BMS and 56 B12D/AG patients.

This study discovered that 42 B12D/BMS patients had significantly higher frequencies of macrocytosis (52.4%), blood Hb (61.9%) and serum iron (26.2%) and vitamin B12 (100.0%) deficiencies, hyperhomocysteinemia (83.3%), and serum GPCA positivity (42.9%) than 442 healthy control subjects. Of 26 anemic B12D/BMS patients, 15 (57.7%) had PA, 5 (19.2%) had macrocytic anemia other than PA, 4 (15.4%) had normocytic anemia, and two (7.7%) had thalassemia trait-induced anemia. We conclude that B12D/BMS patients have significantly higher frequencies of macrocytosis, blood Hb and serum iron and vitamin B12 deficiencies, hyperhomocysteinemia, and serum GPCA positivity than healthy control subjects. Although PA is the most common type of anemia in our B12D/BMS patients, only 15 (35.7%) of 42 B12D/BMS patients have PA, suggesting that not all B12D/BMS patients have PA.

Analysis and/or interpretation of data: Chiang ML, Jin YT, Chiang CP, Sun A

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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