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Original Article

Higher gastric parietal cell antibody titer significantly increases the frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia in patients with burning mouth syndrome

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KEYWORDS

Burning mouth syndrome;
 Macrocytosis;
 Vitamin B12 deficiency;
 Hyperhomocysteinemia;
 Gastric parietal cell antibody

Abstract *Background/purpose:* Our previous study found 109 gastric parietal cell antibody (GPCA)-positive burning mouth syndrome (BMS) patients (so-called GPCA⁺BMS patients in this study) in a group of 884 BMS patients. This study evaluated whether high-titer (GPCA titer \geq 160) GPCA⁺BMS patients had greater frequencies of macrocytosis, anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than low-titer (GPCA titer $<$ 160) GPCA⁺BMS patients or 442 healthy control subjects.

Materials and methods: Complete blood count, serum iron, vitamin B12, folic acid, homocysteine, and GPCA levels in 42 high-titer GPCA⁺BMS patients, 67 low-titer GPCA⁺BMS patients, and 442 healthy control subjects were measured and compared.

Results: We found that 33.3%, 38.1%, 19.0%, 33.3%, 2.4%, and 57.1% of 42 high-titer GPCA⁺BMS patients and 10.4%, 25.4%, 14.9%, 6.0%, 1.5%, and 11.9% of 67 low-titer GPCA⁺BMS patients were diagnosed as having macrocytosis, blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively. Moreover, both 42 high-titer and 67 low-titer GPCA⁺BMS patients had significantly greater frequencies of macrocytosis, blood hemoglobin, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 442 healthy control subjects (all *P*-values $<$ 0.001). In addition, 42 high-titer GPCA⁺BMS patients also had greater frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia than 67 low-titer GPCA⁺BMS patients (all *P*-values $<$ 0.01).

Conclusion: The high-titer GPCA⁺BMS patients have significantly greater frequencies of macrocytosis, anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than healthy control subjects and significantly greater frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia than low-titer GPCA⁺BMS patients.

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Introduction

Our previous study found that 19.3%, 30.3%, 16.5%, 16.5%, 1.8%, and 29.4% of 109 gastric parietal cell antibody (GPCA)-positive burning mouth syndrome (BMS) patients (so-called GPCA⁺BMS patients in this study) have macrocytosis (defined as having the mean corpuscular volume or MCV \geq 100 fL), blood hemoglobin (Hb), iron, vitamin B12, folic acid deficiencies, and hyperhomocysteinemia, respectively.¹ The serum GPCA positivity may cause destruction of gastric parietal cells that produce intrinsic factor and hydrochloric acid. Intrinsic factor and hydrochloric acid are responsible for vitamin B12 and iron absorption, respectively.^{2–6} Moreover, severe vitamin B12 deficiency may result in macrocytosis, anemia, and hyperhomocysteinemia. Thus, GPCA-positive patients are prone to have macrocytosis, anemia, serum vitamin B12 deficiency, and hyperhomocysteinemia.^{1–18}

Our previous study found 109 GPCA⁺ BMS patients in a group of 884 BMS patients.¹ In this study, if GPCA⁺BMS patients' sera were scored as positive for GPCA at a dilution of 10-fold or 20-fold by indirect immunofluorescence, they were regarded as having a GPCA titer of 10 or 20, respectively. By this definition, we found that 42 of 109 GPCA⁺BMS patients have GPCA titers \geq 160 (so-called high-titer GPCA⁺BMS patients) and 67 of 109 GPCA⁺BMS patients have GPCA titers $<$ 160 (so-called low-titer GPCA⁺BMS patients).¹ In this study, complete blood count, serum iron, vitamin B12, folic acid, homocysteine, and serum GPCA levels in 42 high-titer GPCA⁺BMS patients, 67 low-titer

GPCA⁺BMS patients, and 442 healthy control subjects were measured and compared. We tried to find out whether high-titer GPCA⁺BMS patients had greater frequencies of macrocytosis, anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than low-titer GPCA⁺BMS patients or 442 healthy control subjects. In addition, we also evaluated whether 67 low-titer GPCA⁺BMS patients still had significantly higher frequencies of macrocytosis, anemia, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 442 healthy control subjects.

Materials and methods

Subjects

In this study, 42 high-titer GPCA⁺BMS patients (11 men and 31 women, age range 34–80 years, mean age 59.8 ± 10.6 years) and 67 low-titer GPCA⁺BMS patients (15 men and 52 women, age range 21–85 years, mean age 56.2 ± 14.5 years) were selected from 884 BMS patients reported in our previous study.¹ For two BMS patients, one age- (± 2 years of each patient's age) and sex-matched healthy control subject was selected. Thus, 442 age- (± 2 years of each patient's 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.¹⁶ 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.^{1,16–20} The detailed inclusion and exclusion criteria for our BMS patients and healthy control subjects have been described previously.^{1,16–20} 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 GPCA⁺BMS patients and healthy control subjects for the measurement of complete blood count, serum iron, vitamin B12, folic acid, and homocysteine concentrations, and the serum GPCA positivity. All GPCA⁺BMS patients and healthy control subjects signed the informed consent forms before entering the study. This study was reviewed and approved by the Institutional Review Board at the NTUH (201212066RIND).

Determination of blood hemoglobin, iron, vitamin B12, folic acid, and homocysteine concentrations.

The complete blood count and serum iron, vitamin B12, folic acid, and homocysteine concentrations were determined by the routine tests performed in the Department of Laboratory Medicine, NTUH.^{1,16–20}

Determination of serum gastric parietal cell antibody level

The serum GPCA level was detected by the indirect immunofluorescence technique with rat stomach as a substrate as described previously.^{1,16–20} Sera were scored as positive when they produced fluorescence at a dilution of 10-fold or more. Moreover, if GPCA⁺BMS patients' sera were scored as positive for GPCA at a dilution of 10-fold or 20-fold, they were regarded as having a GPCA titer of 10 or 20, respectively. In this study, high-titer GPCA⁺BMS patients were defined as having the GPCA titers ≥ 160 and low-titer GPCA⁺BMS patients were defined as having the GPCA titers < 160 .

Statistical analysis

Comparisons of the mean corpuscular volume (MCV) and mean blood concentrations of Hb, iron, vitamin B12, folic acid, and homocysteine between 42 high-titer GPCA⁺BMS patients or 67 low-titer GPCA⁺BMS patients and 442 healthy control subjects as well as between 42 high-titer GPCA⁺BMS patients and 67 low-titer GPCA⁺BMS patients were performed by Student's *t*-test. The differences in frequencies of macrocytosis, blood Hb, iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia between 42 high-titer GPCA⁺BMS patients or 67 low-titer GPCA⁺BMS patients and 442 healthy control subjects as well as between 42 high-titer GPCA⁺BMS patients and 67 low-titer GPCA⁺BMS patients were compared by chi-square test. The result was considered to be significant if the *P*-value was less than 0.05.

Results

The MCV, mean blood concentrations of Hb, iron, vitamin B12, folic acid, and homocysteine in 42 high-titer GPCA⁺BMS patients, 67 low-titer GPCA⁺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 that 42 high-titer GPCA⁺BMS patients had significantly lower mean blood Hb (for men and women), iron (for men and women), and vitamin B12 levels as well as significantly higher MCV and mean serum homocysteine levels than 442 healthy control subjects (all *P*-values < 0.001 , Table 1) and significantly lower mean serum iron (for men only) and vitamin B12 levels as well as significantly higher mean serum homocysteine levels than 67 low-titer GPCA⁺BMS patients (all *P*-values < 0.01 , Table 1). Moreover, 67 low-titer GPCA⁺BMS patients had significantly lower mean blood Hb (for men and women) than 442 healthy control subjects (both *P*-values < 0.01 , Table 1).

According to the World Health Organization (WHO) criteria, macrocytosis of erythrocyte was defined as having an MCV ≥ 100 fL,^{7–9} and men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.²¹ Furthermore, patients with the serum iron level < 60 μ g/dL,²² the serum vitamin B12 level < 200 pg/mL,²³ or the folic acid level < 4 ng/mL²⁴ were defined as having iron, vitamin B12 or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level > 12.3 μ M (which was the mean serum homocysteine level of healthy control subjects plus two standard deviations) were defined as having hyperhomocysteinemia.¹⁶ By the above-mentioned definitions, we found that 33.3%, 38.1%, 19.0%, 33.3%, 2.4%, and 57.1% of 42 high-titer GPCA⁺BMS patients and 10.4%, 25.4%, 14.9%, 6.0%, 1.5%, and 11.9% of 67 low-titer GPCA⁺BMS patients were diagnosed as having macrocytosis, blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia, respectively. Moreover, both 42 high-titer and 67 low-titer GPCA⁺BMS patients had significantly greater frequencies of macrocytosis, blood hemoglobin, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 442 healthy control subjects (all *P*-values < 0.001 , Table 2). In addition, 42 high-titer GPCA⁺BMS patients also had greater frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia than 67 low-titer GPCA⁺BMS patients (all *P*-values < 0.01 , Table 2).

Discussion

The main finding of this study was that 42 high-titer GPCA⁺BMS patients had significantly greater frequencies of macrocytosis, blood hemoglobin, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 442 healthy control subjects. In addition, 42 high-titer GPCA⁺BMS patients also had greater frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia than 67 low-titer GPCA⁺BMS patients. Although the frequencies of anemia and serum iron deficiency was higher in 42 high-titer

Table 1 Comparisons of mean corpuscular volume (MCV), mean blood concentrations of hemoglobin (Hb), iron, vitamin B12, folic acid, and homocysteine between 42 high-titer (gastric parietal cell antibody or GPCA titer ≥ 160) GPCA-positive burning mouth syndrome (GPCA⁺BMS) patients or 67 low-titer (GPCA titer < 160) GPCA⁺BMS patients and 442 healthy control subjects as well as between 42 high-titer GPCA⁺BMS patients and 67 low-titer GPCA⁺BMS patients.

Group	MCV (fL)	Hb (g/dL)		Iron ($\mu\text{g/dL}$)		Vitamin B12 (pg/mL)	Folic acid (ng/mL)	Homocysteine (μM)
		Men	Women	Men	Women			
High-titer GPCA ⁺ BMS patients (n = 42)	93.5 \pm 8.8	13.5 \pm 1.2 (n = 11)	12.9 \pm 1.1 (n = 31)	73.6 \pm 15.8 (n = 11)	79.1 \pm 24.8 (n = 31)	324.1 \pm 179.5	15.3 \pm 6.1	14.5 \pm 9.3
^a P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.517	<0.001
^b P-value	0.086	0.147	>0.999	0.003	0.050	<0.001	0.684	<0.001
Low-titer GPCA ⁺ BMS patients (n = 67)	90.6 \pm 8.3	14.4 \pm 1.7 (n = 15)	12.9 \pm 1.1 (n = 52)	101.6 \pm 25.1 (n = 15)	91.0 \pm 27.3 (n = 52)	729.2 \pm 247.9	14.8 \pm 6.3	8.5 \pm 3.1
^a P-value	0.735	0.009	<0.001	0.638	0.094	0.234	>0.999	0.483
Healthy control subjects (n = 442)	90.4 \pm 3.6	15.1 \pm 0.8 (n = 106)	13.5 \pm 0.7 (n = 336)	105.2 \pm 28.0 (n = 106)	97.8 \pm 27.2 (n = 336)	694.2 \pm 220.2	14.7 \pm 5.7	8.3 \pm 2.0

^a Comparisons of means of parameters between 42 high-titer GPCA⁺BMS patients or 67 low-titer GPCA⁺BMS patients and 442 healthy control subjects by Student's *t*-test.

^b Comparisons of means of parameters between 42 high-titer GPCA⁺BMS patients and 67 low-titer GPCA⁺BMS patients by Student's *t*-test.

Table 2 Comparisons of frequencies of macrocytosis (mean corpuscular volume or MCV ≥ 100 fL), blood hemoglobin, iron, vitamin B12, and folic acid deficiencies, and hyperhomocysteinemia between 42 high-titer (gastric parietal cell antibody or GPCA titer ≥ 160) GPCA-positive burning mouth syndrome (GPCA⁺BMS) patients or 67 low-titer (GPCA titer < 160) GPCA⁺BMS patients and 442 healthy control subjects as well as between 42 high-titer GPCA⁺BMS patients and 67 low-titer GPCA⁺BMS patients.

Group	Patient number (%)					
	Macrocytosis (MCV ≥ 100 fL)	Hemoglobin deficiency (Men < 13 g/dL, women < 12 g/dL)	Iron deficiency (< 60 $\mu\text{g/dL}$)	Vitamin B12 deficiency (< 200 pg/mL)	Folic acid deficiency (< 4 ng/mL)	Hyperhomocysteinemia (> 12.3 μM)
High-titer GPCA ⁺ BMS patients (n = 42)	14 (33.3)	16 (38.1)	8 (19.0)	14 (33.3)	1 (2.4)	24 (57.1)
^a P-value	<0.001	<0.001	<0.001	<0.001	0.142	<0.001
^b P-value	0.007	0.233	0.765	<0.001	0.691	<0.001
Low-titer GPCA ⁺ BMS patients (n = 67)	7 (10.4)	17 (25.4)	10 (14.9)	4 (6.0)	1 (1.5)	8 (11.9)
^a P-value	<0.001	<0.001	<0.001	<0.001	0.275	<0.001
Healthy control subjects (n = 442)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.5)

^a Comparisons of frequencies of parameters between 42 high-titer GPCA⁺BMS patients or 67 low-titer GPCA⁺BMS patients and 442 healthy control subjects by chi-square test.

^b Comparisons of frequencies of parameters between 42 high-titer GPCA⁺BMS patients and 67 low-titer GPCA⁺BMS patients by chi-square test.

GPCA⁺BMS patients (38.1% and 19.0%, respectively) than in 67 low-titer GPCA⁺BMS patients (25.4% and 14.9%, respectively), the differences were not significant (Table 2). The high-titer GPCA⁺BMS patients were supposed to have more destruction of their gastric parietal cells and thus they were more likely to have severer deficiencies of intrinsic factors and hydrochloric acid, finally resulting in having higher frequencies of vitamin B12 and iron deficiencies than low-titer GPCA⁺BMS patients.^{2–6} The vitamin B12 is related to DNA synthesis and red blood cell proliferation and generation.^{3,4,6} The iron is a component of Hb (other three components are protoporphyrin IX, α -globin, and β -globin).^{19,20} Therefore, severer deficiencies of vitamin B12 and iron could lead to greater frequency of Hb deficiency or anemia in 42 high-titer GPCA⁺BMS patients (38.1%) than in 67 low-titer GPCA⁺BMS patients (25.4%) (Table 2).

In this study, of 14 high-titer GPCA⁺BMS patients with macrocytosis, 14 had vitamin B12 deficiency and none had folic acid deficiency. Moreover, of 7 low-titer GPCA⁺BMS patients with macrocytosis, 3 had vitamin B12 deficiency (vitamin B12 < 200 pg/mL), the other 4 had serum vitamin B12 level between 200 pg/mL and 500 pg/mL, and none had folic acid deficiency. These findings suggest that vitamin B12 deficiency is the main contributing factor causing macrocytosis in both high-titer and low-titer GPCA⁺BMS patients.^{6–9} The frequency of vitamin B12 deficiency was significantly higher in 42 high-titer GPCA⁺BMS patients (33.3%) than in low-titer GPCA⁺BMS patients (6.0%). This could explain why a greater frequency of macrocytosis was noted in 42 high-titer GPCA⁺BMS patients (33.3%) than in 67 low-titer GPCA⁺BMS patients (10.4%) (Table 2).

Homocysteine is formed during methionine metabolism.²⁵ Both vitamin B12 and folic acid function as co-enzymes for the conversion of homocysteine to methionine.²⁶ Therefore, patients with vitamin B12 and/or folic acid deficiencies may have hyperhomocysteinemia. Supplement therapy with folic acid, vitamin B12, and vitamin B6 can reduce blood homocysteine levels.²⁷ Our previous studies also demonstrated that supplementations with vitamin BC capsules plus corresponding deficient vitamin B12 and/or folic acid can reduce the abnormally high serum homocysteine level to significantly lower levels in patients with either atrophic glossitis or BMS.^{28,29} This study demonstrated a higher frequency of hyperhomocysteinemia in high-titer GPCA⁺BMS patients (57.1%) than in low-titer GPCA⁺BMS patients (11.9%). Of the 24 high-titer GPCA⁺BMS patients with hyperhomocysteinemia, 13 (54.2%) had vitamin B12 deficiency and one (4.2%) had folic acid deficiency. Of the 8 low-titer GPCA⁺BMS patients with hyperhomocysteinemia, 4 (50.0%) had vitamin B12 deficiency and none (0.0%) had folic acid deficiency. These findings suggest that GPCA-induced vitamin B12 deficiency is the major contributing factor for hyperhomocysteinemia in 24 high-titer and 8 low-titer GPCA⁺BMS patients.^{25–27} Thus, the significantly higher frequency vitamin B12 deficiency in 42 high-titer GPCA⁺BMS patients (33.3%) than in 67 low-titer GPCA⁺BMS patients (6.0%) could explain why a greater frequency of hyperhomocysteinemia was found in 42 high-titer GPCA⁺BMS patients (57.1%) than in 67 low-titer GPCA⁺BMS patients (11.9%) (Table 2).

This study discovered that both 42 high-titer and 67 low-titer GPCA⁺BMS patients had significantly greater

frequencies of macrocytosis, blood hemoglobin, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than 442 healthy control subjects. In addition, 42 high-titer GPCA⁺BMS patients also had greater frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia than 67 low-titer GPCA⁺BMS patients. Therefore, we conclude that the high-titer GPCA⁺BMS patients have significantly greater frequencies of macrocytosis, blood hemoglobin, serum iron and vitamin B12 deficiencies, and hyperhomocysteinemia than healthy control subjects and significantly greater frequencies of macrocytosis, serum vitamin B12 deficiency, and hyperhomocysteinemia than low-titer GPCA⁺BMS patients.

Declaration of competing interest

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

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