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ORIGINAL ARTICLE

Significant association of hematinic deficiencies and high blood homocysteine levels with burning mouth syndrome

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KEYWORDS
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Background/Purpose: Burning mouth syndrome (BMS) is characterized by a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations. In this study, we evaluated whether there was an intimate association of the deficiency of hemoglobin (Hb), iron, vitamin B12, or folic acid; high blood homocysteine level; and serum gastric parietal cell antibody (GPCA) positivity with BMS.

Methods: Blood Hb, iron, vitamin B12, folic acid, and homocysteine concentrations and the serum GPCA level were measured in 399 BMS patients and compared with the corresponding levels in 399 age- and sex-matched healthy control individuals.

Results: We found that 89 (22.3%), 81 (20.3%), 10 (2.5%), and six (1.5%) BMS patients had deficiencies of Hb (men: <13 g/dL, women: <12 g/dL), iron (<60 μg/dL), vitamin B12 (<200 pg/mL), and folic acid (<4 ng/mL), respectively. Moreover, 89 (22.3%) BMS patients had abnormally high blood homocysteine level and 53 (13.3%) had serum GPCA positivity. BMS patients had a significantly higher frequency of Hb, iron, or vitamin B12 deficiency; of abnormally elevated blood homocysteine level; or of serum GPCA positivity than the healthy control group (all $p < 0.001$ except for vitamin B12 deficiency, for which $p = 0.004$). However, no significant difference in frequency of folic acid deficiency ($p = 0.129$) was found between BMS patients and healthy control individuals.

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Conclusion: We conclude that there is a significant association of deficiency of Hb, iron, and vitamin B12; abnormally high blood homocysteine level; and serum GPCA positivity with BMS.

Introduction

Burning mouth syndrome (BMS) is typically described by the patients as a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.[1] BMS affects 2−3% of adults and 14% of postmenopausal women. Asians have a higher risk than Caucasians. Women are more likely to have BMS than men. Its prevalence increases with advancing age. BMS is also one of the most common disorders seen in oral mucosal disease clinic.[1,2]

Both local and systemic factors are involved in the etiology of BMS. Local factors include xerostomia, oral candidiasis, oral submucous fibrosis, poorly fitting prosthesis, etc. Systemic factors include deficiencies of thiamin, riboflavin, niacin, vitamin 12 (pernicious anemia), folic acid, iron (iron-deficiency anemia and Plummer−Vinson syndrome), and estrogen; diabetes mellitus; hypothyroidism; Sjogren's syndrome; anxiety; psychosocial stress; depression; Parkinson's disease; and others.[1−3] Majority of these local or systemic factors have not been proved in a well-controlled study.

The tongue, especially the tip and lateral borders, is most commonly affected by the BMS.[2] In this study, the symptoms (such as dry mouth, burning sensation, numbness, and loss or dysfunction of taste) and signs (such as varicosity and candidiasis) of the tongue, blood chemistry [including blood levels of hemoglobin (Hb), iron, vitamin B12, folic acid, and homocysteine], and serum gastric parietal cell antibody (GPCA) level in 399 BMS patients were inquired, examined, and recorded. These data were compared with corresponding data in 399 age- and sex-matched healthy control individuals without oral mucosal and systemic diseases. Statistical analyses were performed to assess whether there was an intimate association of deficiency of any specific hematinic factors, abnormally high blood homocysteine level, and serum GPCA positivity with BMS.

Patients and methods

Participants

The study group consisted of 399 patients (95 men and 304 women, age range 28−91 years, mean 59.7 ± 13.9 years) with BMS. The normal control group consisted of 399 age- (±2 years of each patient's age) and sex-matched healthy control individuals (95 men and 304 women, age range 31−90 years, mean 59.6 ± 14.0 years). All the patients and control individuals were seen consecutively, diagnosed, and treated in the Department of Dentistry of National Taiwan University Hospital from July 2007 to June 2011. Patients were diagnosed as having BMS when they complained of burning sensation of the oral mucosa but no apparent clinical oral mucosal abnormality was found (Fig. 1A and 1B). However, BMS patients with areca quid chewing habit or autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, pemphigus vulgaris, and cicatricial pemphigoid) were excluded. In addition, BMS patients with serum creatinine concentrations indicative of renal dysfunction (men, >131 μmol/L; women, >115 μmol/L) and those who reported a history of stroke, heavy alcohol use, or diseases of the liver, kidney, or coronary arteries were also excluded.[4] Healthy control individuals had either dental caries or periodontal diseases, but no oral mucosal or systemic diseases. None of the BMS patients had taken any prescription medication for BMS at least 3 months prior to entering the study. For BMS patients and healthy controls, the symptoms (such as dry mouth, burning sensation, numbness, and loss or dysfunction of taste) and signs [such as candidiasis and varicosity (Fig. 1C)] of the tongue were inquired, examined, and recorded. Blood samples were drawn from BMS patients and healthy controls to measure the blood Hb, iron, vitamin B12, folic acid, and homocysteine concentrations and the serum GPCA levels. This study was reviewed and approved by the Institutional Review Board at the National Taiwan University Hospital.

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

Concentrations of blood Hb, iron, vitamin B12, folic acid, and homocysteine were determined by the routine tests performed in the Department of Laboratory Medicine of National Taiwan University Hospital.

Determination of serum GPCA level

Serum GPCA level was detected by the indirect immunofluorescence technique with rat stomach as a substrate, as described previously.[5,6] In brief, 5 μm thick cryostat sections of substrate tissues on slides were reacted with serially diluted patients' and control individuals' sera in a moist chamber at room temperature for 30 minutes. The initial dilution of the patients' and control individuals' sera was 1:20 with phosphate-buffered saline (PBS). After washing, the sections were incubated with fluorescein-isothiocyanate-labeled goat antihuman immunoglobulin G (IgG) antiserum (Boehringer Mannheim Biochemicals, Indianapolis, IN, USA), which had been prediluted and kept in a dropper vial by the manufacturer and was ready to use for another 30 minutes. The sections were washed again, mounted with buffered glycerine, and examined with an Olympus fluorescence microscope (Olympus, Tokyo,

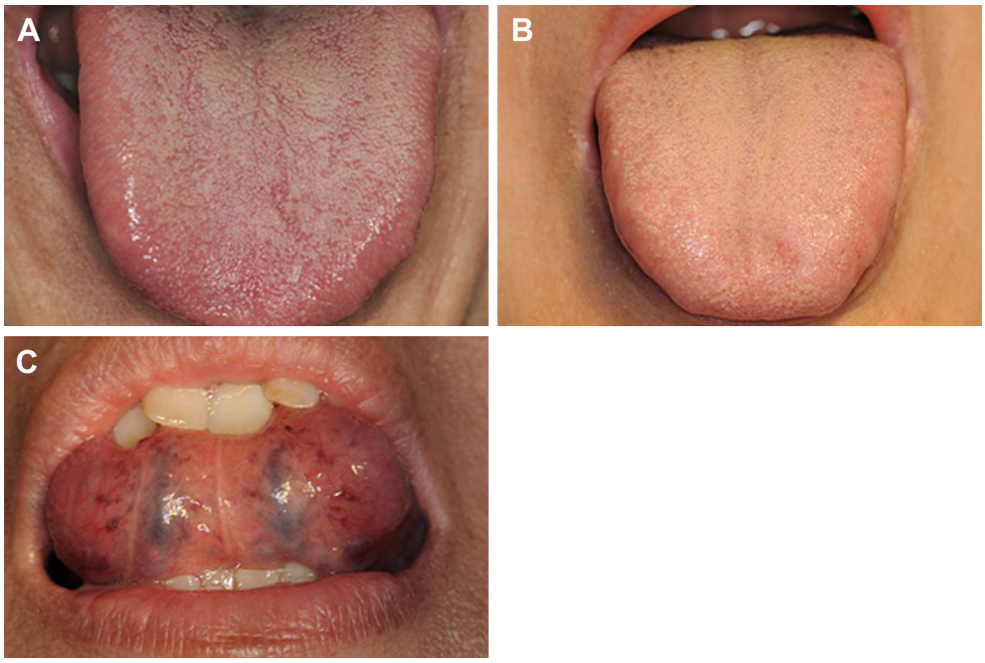

Figure 1 Clinical photographs of the tongue and lingual varicosity in patients with burning mouth syndrome. (A) The tongue of a 61-year-old female patient showing no definite lesion on the dorsal surface. (B) The tongue of a 56-year-old female patient showing no apparent alteration on the dorsal surface. (C) Lingual varicosity on the ventral surface of the tongue in a 62-year-old female patient.

Japan). Sera were scored as positive when they produced fluorescence at a dilution of 20-fold or more.

Diagnosis of oral candidiasis

For each BMS patient, two exfoliative cytologic slides were prepared from the dorsal surface of the tongue. One slide was stained with periodic acid-Schiff (PAS) method and examined for the presence of candidal hyphae and yeasts. The presence of bright magenta-colored hyphae or pseudohyphae confirmed the diagnosis of candidiasis. The other slide was prepared with 20% potassium hydroxide for the rapid identification of the fungal organisms. The dorsal surface of the tongue was diagnosed as having candidiasis when either one of the cytologic preparations was positive for candidal hyphae or yeasts.[1] Exfoliative cytologic slides were prepared from the dorsal surface of the normal tongues of only a few healthy control individuals. These slides were stained with PAS or treated with 20% potassium hydroxide and then examined by light microscopy for the presence of *Candida albicans*.

Statistical analysis

Comparisons of the mean blood levels of Hb, iron, vitamin B12, folic acid, and homocysteine between 399 AG patients and 399 age- and sex- matched healthy control individuals were performed by Student *t* test. The differences in frequency of Hb, iron, vitamin B12, or folic acid deficiency; of abnormally high blood homocysteine level; or of serum GPCA positivity between 399 BMS patients and 399 healthy control individuals or our previously reported 176 patients with atrophic glossitis (AG)[7] were compared by chi-square test. In addition, the differences in frequency of the presence of symptoms or signs between BMS patients and healthy control individuals or AG patients were also compared by chi-square test. The result was considered to be significant if $p < 0.05$.

Results

The mean blood concentrations of Hb, iron, vitamin B12, folic acid, and homocysteine in 399 BMS patients and 399 age- and sex-matched healthy control individuals are shown in Table 1. Because men usually have higher blood levels of Hb and iron than women, these two mean levels were calculated separately for men and women. We found that BMS patients had significantly lower mean Hb ($p < 0.001$ for both men and women) and iron levels ($p < 0.001$ for both men and women) and significantly higher mean homocysteine levels ($p < 0.001$) than healthy controls (Table 1). However, no significant difference in the mean serum vitamin B12 ($p = 0.522$) or folic acid level ($p = 0.137$) was demonstrated between them (Table 1).

According to the World Health Organization criteria, men with Hb <13 g/dL and women with Hb <12 g/dL were defined as having Hb deficiency or anemia.[8] Furthermore, patients with serum iron level <60 μg/dL,[9] serum vitamin B12 level <200 pg/mL (148 pmol/L),[4] or folic acid level <4 ng/mL (10 nmol/L)[10] were defined as having iron, vitamin B12, or folic acid deficiency, respectively. In addition, patients with blood homocysteine level >12.4 μmol/L (which was the mean blood homocysteine level of healthy controls plus two standard deviations) were defined as

Table 1 Mean blood concentrations of Hb, iron, vitamin B12, folic acid, and homocysteine in 399 patients with BMS and in 399 age- and sex-matched healthy control individuals.

	Patients with BMS ($n = 399$)		Healthy control individuals ($n = 399$)		p (Student t test)
	Mean ± SD	Range	Mean ± SD	Range	
Hb (g/dL)					
Men ($n = 95$)	13.7 ± 1.5	7.8–16.6	14.9 ± 0.7	13.2–16.7	<0.001[a]
Women ($n = 304$)	12.6 ± 1.3	7.1–15.6	13.4 ± 0.8	12.0–15.4	<0.001[a]
Iron (μg/dL)					
Men ($n = 95$)	90.0 ± 29.7	33–158	104.9 ± 23.4	65–160	<0.001[a]
Women ($n = 304$)	80.9 ± 23.4	10–160	96.2 ± 23.8	56–160	<0.001[a]
Vitamin B12 (pg/mL)	677.5 ± 280.0	150–1000	688.3 ± 186.5	265–998	0.522
Folic acid (ng/mL)	13.8 ± 6.3	2.9–24.0	14.4 ± 5.0	5.8–24.0	0.137
Homocysteine (μmol/L)	10.9 ± 7.6	4.8–133.1	8.6 ± 1.9	4.6–15.8	<0.001[a]

BMS = burning mouth syndrome; Hb = hemoglobin.
[a] Comparisons of the mean blood levels of Hb, iron, vitamin B12, folic acid and homocysteine between 399 BMS patients and 399 age- and sex-matched healthy control individuals by Student t test with $p < 0.05$.

having abnormally high homocysteine level. By the above-mentioned definitions, 89 (22.3%), 81 (20.3%), 10 (2.5%), and six (1.5%) BMS patients were diagnosed as having Hb, iron, vitamin B12, and folic acid deficiencies, respectively (Table 2). Moreover, 89 (22.3%) BMS patients had abnormally high blood homocysteine level and 53 (13.3%) had serum GPCA positivity (Table 2). BMS patients had a significantly higher frequency of Hb, iron, or vitamin B12 deficiency; of abnormally elevated blood homocysteine level; or of serum GPCA positivity than healthy control individuals (all $p < 0.001$ except for vitamin B12 deficiency, for which $p = 0.004$; Table 2). However, no significant difference in frequency of folic acid deficiency ($p = 0.129$) was found between BMS patients and healthy control individuals.

When the frequencies of Hb, iron, vitamin B12, or folic acid deficiency; of high blood homocysteine level; and of serum GPCA positivity were further compared between 399 BMS patients and our previously reported 176 AG patients,[7] we found that AG patients had a higher frequency of vitamin B12 deficiency ($p = 0.012$) and of GPCA positivity ($p < 0.001$) than BMS patients (Table 3).

The tongue-associated symptoms and signs in 399 BMS patients and 399 age- and sex-matched healthy control individuals are shown in Table 4. Burning sensation of the tongue (100%) was found to be the most common symptom and lingual varicosity (92.5%) was the most frequent sign in 399 BMS patients. In addition, BMS patients had significantly higher frequencies of the tongue-associated symptoms and signs than healthy control individuals (all $p < 0.001$; Table 4). Because exfoliative cytologic slides were prepared for only a few healthy control individuals, we did not know the exact *Candida* prevalence in healthy control individuals.

In addition, if these tongue-associated symptoms and signs were further compared between 399 BMS patients and 176 AG patients,[7] we found that AG patients had a higher

Table 2 Number and percentage of individuals with hemoglobin, iron, vitamin B12, or folic acid deficiency; with abnormally high homocysteine level; or with serum GPCA positivity in 399 patients with BMS and in 399 age- and sex-matched healthy control individuals.

Factor	Patients with BMS ($n = 399$)	Healthy control individuals ($n = 399$)	p (chi-square test)
Hemoglobin deficiency (men <13 g/dL, women <12 g/dL)	89 (22.3%)	0 (0%)	<0.001[a]
Iron deficiency (<60 μg/dL)	81 (20.3%)	12 (3.0%)	<0.001[a]
Vitamin B12 deficiency (<200 pg/mL)	10 (2.5%)	0 (0%)	0.004[a]
Folic acid deficiency (<4 ng/mL)	6 (1.5%)	1 (0.3%)	0.129
High homocysteine level[b] (>12.4 μmol/L)	89 (22.3%)	19 (4.8%)	<0.001[a]
GPCA positivity	53 (13.3%)	8 (2.0%)	<0.001[a]

BMS = burning mouth syndrome; GPCA = gastric parietal cell antibody.
[a] Comparison of frequency of hemoglobin, iron, vitamin B12, or folic acid deficiency; of abnormally high blood homocysteine level; or of serum GPCA positivity between 399 BMS patients and 399 age- and sex- matched healthy control individuals by chi-square test with $p < 0.05$.
[b] High homocysteine level was defined as patients with the homocysteine level greater than the mean of homocysteine level of healthy control individuals plus two standard deviations.

Table 3 Number and percentage of individuals with hemoglobin, iron, vitamin B12, or folic acid deficiency; with abnormally high homocysteine level; or with serum GPCA positivity in 399 patients with BMS and in previously reported 176 patients with AG.[7]

Factor	Patients with BMS ($n = 399$)	Patients with AG ($n = 176$)	p (chi-square test)
Hemoglobin deficiency (men <13 g/dL, women <12 g/dL)	89 (22.3%)	39 (22.2%)	0.944
Iron deficiency (<60 μg/dL)	81 (20.3%)	47 (26.7%)	0.111
Vitamin B12 deficiency (<200 pg/mL)	10 (2.5%)	13 (7.4%)	0.012[a]
Folic acid deficiency (<4 ng/mL)	6 (1.5%)	3 (1.7%)	0.853
High homocysteine level[b] (>12.4 μmol/L)	89 (22.3%)	38 (21.6%)	0.935
GPCA positivity	53 (13.3%)	47 (26.7%)	<0.001[a]

AG = atrophic glossitis; BMS = burning mouth syndrome; GPCA = gastric parietal cell antibody.
[a] Comparison of frequency of hemoglobin, iron, vitamin B12, or folic acid deficiency; of abnormally high blood homocysteine level; or of serum GPCA positivity between 399 BMS patients and 176 AG patients by chi-square test with $p < 0.05$.
[b] High homocysteine level was defined as patients with the homocysteine level greater than the mean of homocysteine level of healthy control individuals plus two standard deviations.

frequency of numbness of tongue ($p = 0.004$), dysfunction of taste ($p = 0.043$), or lingual varicosity ($p = 0.004$) than BMS patients (Table 5).

Discussion

This study showed that BMS patients had significantly higher frequencies of Hb, iron, and vitamin B12 deficiency; of abnormally elevated blood homocysteine level; and of serum GPCA positivity than healthy control individuals. Both BMS and AG patients complained of burning sensation of the tongue.[1] When BMS and AG patients were further compared, we demonstrated a significantly higher frequency of vitamin B12 deficiency and of serum GPCA positivity in AG patients than in BMS patients. However, there was no significant difference in the frequency of Hb or iron deficiency or in the frequency of abnormally high blood homocysteine level between AG and BMS patients. Patients with GPCA positivity had destruction of gastric parietal cells by an autoimmune mechanism, resulting in deficiency of intrinsic factor, lack of absorption of vitamin B12 from small intestine, and finally vitamin B12 deficiency.[1] This can explain why patients with GPCA positivity usually also have lower serum vitamin B12 level. Because vitamin B12 deficiency and GPCA positivity are associated with pernicious anemia, our findings suggest that AG patients may be more likely to have pernicious anemia than BMS patients. In fact, if pernicious anemia is defined as the presence of an Hb concentration of <13 g⁄dL for men and <12 g⁄dL for women, a mean corpuscular volume ≥100 fL, and a low serum vitamin B12 level (<200 pg/mL),[11] we discovered that only 13 (7.4%) of the 176 AG patients[7] and 10 (2.5%) of the 399 BMS patients could be classified as having pernicious anemia. Therefore, our data also support the fact that there is a higher frequency of pernicious anemia in AG patients than in BMS patients.

Higher blood homocysteine levels are associated with increased rates of coronary heart disease and stroke, because high blood homocysteine level can cause oxidative stress, damage endothelium, and enhance thrombogenicity in experimental studies.[12–15] This study found an abnormally higher blood homocysteine level in 22.3% of BMS patients, whereas it could be discovered in only 4.8% of healthy control individuals. This high blood homocysteine level in BMS patients could be due to deficiency in folic acid, vitamin B6, and vitamin B12, because a previous study has shown that a supplementation with folic acid, vitamin B6, and vitamin B12 can reduce blood homocysteine levels.[12] Indeed, deficiency of vitamin B12 was more

Table 4 Tongue-associated symptoms and signs in 399 patients with BMS and in 399 age- and sex-matched healthy control individuals.

Symptoms and signs of the tongue	Patients with BMS ($n = 399$)	Healthy control individuals ($n = 399$)	p (chi-square test)
Dry mouth	302 (75.7%)	0 (0%)	<0.001[a]
Burning sensation	399 (100.0%)	0 (0%)	<0.001[a]
Numbness	175 (43.9%)	0 (0%)	<0.001[a]
Dysfunction of taste	79 (19.8%)	0 (0%)	<0.001[a]
Varicosity	369 (92.5%)	0 (0%)	<0.001[a]
Candidiasis	32 (8.0%)	Unknown	

BMS = burning mouth syndrome.
[a] Comparison of frequency of the presence of symptom or sign between 399 BMS patients and 399 age- and sex-matched healthy control individuals by chi-square test with $p < 0.05$.

Table 5 Tongue-associated symptoms and signs in 399 patients with BMS and in previously reported 176 patients with AG.[7]

Symptoms and signs of the tongue	Patients with BMS ($n = 399$)	Patients with AG ($n = 176$)	p (chi-square test)
Dry mouth	302 (75.7%)	139 (79.0%)	0.452
Burning sensation	399 (100.0%)	176 (100%)	NSD
Numbness	175 (43.9%)	101 (57.4%)	0.004[a]
Dysfunction of taste	79 (19.8%)	49 (27.8%)	0.043[a]
Varicosity	369 (92.5%)	174 (98.9%)	0.004[a]
Candidiasis	32 (8.0%)	22 (12.5%)	0.123

AG = atrophic glossitis; BMS = burning mouth syndrome; NSD = no significant difference.
[a] Comparison of frequency of the presence of symptom or sign between 399 BMS patients and 176 AG patients by chi-square test with $p < 0.05$.

frequently detected in BMS patients than in healthy controls in this study. The deficiency of vitamin B12 finally resulted in high blood homocysteine level in BMS patients.

Burning sensation, dry mouth, and numbness of the tongue were the three most common symptoms of BMS patients, and could be found in 100%, 75.7%, and 43.9% of BMS patients in this study, respectively. Iron and vitamin B12 are related to the health of oral epithelium. Long-term dry mouth and iron or vitamin B12 deficiency may cause at least partial atrophy of the tongue epithelium in BMS patients, although the alteration is so subtle that it cannot be recognized by clinical visual examination. Therefore, the spicy molecules in the saliva could easily diffuse through the atrophic epithelium into the subepithelial connective tissue of the tongue mucosa, irritate the free sensory nerve endings, and in turn induce burning sensation and numbness of the tongue.

Loss or dysfunction of taste was a minor symptom of BMS and could be found in 19.8% of BMS patients in the present study. The chemical substances should be dissolved in saliva because the taste cells in taste buds can perceive only the dissolved substances. Xerostomia was described in 75.7% of the BMS patients. Decreased secretion of saliva in turn resulted in loss or dysfunction of taste in BMS patients. Moreover, oral candidiasis, vitamin B12 deficiency, iron deficiency, and medication are all associated with loss or dysfunction of taste.[1,16] In addition, Femiano et al analyzed the causes of taste disturbance in BMS patients. Of 142 BMS patients, 61 revealed the habitual use of drugs having a documented interference with taste perception, 35 had pathologies or a previous history of use of drugs that are known to affect the gustatory system, and the remaining 46 patients had no associated pathology or habitual use of drugs.[17]

Varicosities are abnormally dilated and tortuous veins that are often found on the ventral surface of the tongue in aged individuals due to the age-related loss of connective tissue tone supporting the veins.[1] Moreover, xerostomia is a common problem that has been reported in 25% of older adults.[1] A number of developmental, iatrogenic, systemic, and local factors may play a role in the cause of xerostomia. However, xerostomia in older adults is more likely the result of medications, because aged patients are prone to taking drugs associated with xerostomia to overcome their systemic or psychotic disorders.[1] In this study, the mean age of 399 BMS patients was 59.7 years. Therefore, it was not surprising to find lingual varicosity in 92.5% and dry mouth in 75.7% of 399 BMS patients. Because normal and sufficient saliva can provide cleansing and antimicrobial activity, there is an increased prevalence of oral candidiasis in patients with xerostomia.[1] We suggest that the candidiasis on the tongue surfaces of our 32 (8.0%) BMS patients may be at least partially due to the high incidence (75.7%) of dry mouth.

Our results demonstrated that 22.3%, 20.3%, and 2.5% of our 399 BMS patients had deficiencies of Hb, iron, and vitamin B12, respectively. Moreover, 22.3% and 13.3% of our 399 BMS patients had abnormally high blood homocysteine level and serum GPCA positivity, respectively. We also found a significantly higher frequency of Hb, iron, or vitamin B12 deficiency; of abnormally elevated blood homocysteine level; or of serum GPCA positivity in our 399 BMS patients than in 399 healthy control individuals. These findings suggest that there is a significant association of deficiency of Hb, iron, and vitamin B12; abnormally high blood homocysteine level; and serum GPCA positivity with BMS.

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