Hematinic deficiencies and anemia statuses in oral mucosal disease patients with folic acid deficiency

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KEYWORDS
folic acid; macrocytic anemia; microcytic anemia; normocytic anemia; pernicious anemia; vitamin B12

Background/Purpose: Folic acid deficiency (FAD) may result in macrocytic anemia. This study assessed the hematinic deficiencies and anemia statuses in oral mucosal disease patients with FAD (defined as folic acid < 6 ng/mL).

Methods: The blood hemoglobin (Hb), iron, vitamin B12, and folic acid concentrations, serum gastric parietal cell antibody level, and mean corpuscular volume (MCV) in 198 oral mucosal disease patients with FAD were measured. Based on World Health Organization (WHO) criteria, anemia or Hb deficiency was defined as having an Hb concentration of <13 g/dL for men and <12 g/dL for women. In this study, macrocytic anemia due to FAD was defined as having an MCV ≥100 fL and folic acid <6 ng/mL; pernicious anemia as having MCV ≥100 fL, vitamin B12 < 200 pg/mL, and serum gastric parietal cell antibody positivity; iron deficiency anemia as having MCV <80 fL and iron <60 μg/dL; and thalassemia trait as having MCV <74 fL, red blood cell (RBC) count > 5.0 × 10¹²/L, and Mentzer index (MCV/RBC) < 13.

Results: We found that by WHO definitions, 73 (36.9%), 41 (20.7%), and 10 (5.1%) of our 198 FAD patients had concomitant Hb, iron, and vitamin B12 deficiencies, respectively. Of 73 anemic FAD patients, three had macrocytic anemia due to FAD, one had pernicious anemia, 14 had iron deficiency anemia, eight had thalassemia trait, and the resting 47 had normocytic anemia.

Conclusion: In addition to macrocytic anemia (2.0%), FAD patients may have concomitant normocytic (23.7%) or microcytic (11.1%) anemia.

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Introduction

Folic acid is an important B vitamin that is necessary for DNA synthesis of red blood cells (RBCs). Folic acid deficiency (FAD) may result in macrocytosis that is defined as having a mean corpuscular volume (MCV) ≥ 100 fL.1-3 Patients with FAD or macrocytosis may or may not have anemia. FAD results from poor nutritional intake, malabsorption, hepatobiliary dysfunction, increased folate catabolism, and medication (e.g., methotrexate, 5-fluorouracil, phenytoin).2 Moreover, the etiologies of macrocytic anemia include nutritional deficiencies (vitamin B12 and folic acid), drugs (e.g., chemotherapeutic, antiretroviral, and antimicrobial agents), primary bone marrow disorders (e.g., myelodysplasia and leukemia), and other chronic illness (such as alcoholism and hypothyroidism).1-3 Because multiple causes are involved in FAD and macrocytosis, it is interesting to know the frequency of macrocytosis or macrocytic anemia in oral mucosal disease patients with FAD.

In our oral mucosal disease clinic, there are many patients with burning mouth syndrome (BMS), atrophic glossitis (AG), recurrent aphthous ulcerations (RAUs), or oral lichen planus (OLP). For these patients, complete blood count and examination of serum iron, vitamin B12, folic acid, and homocysteine levels are usually ordered to check whether these patients have microcytic, normocytic, or macrocytic anemia, thalassemia, and deficiencies of hematinsics.4-6 If patients with oral mucosal disease have hematinic deficiencies, multiple hematinic supplement therapy frequently results in correction of anemic status and improvement of oral symptoms and signs.15,16 Although not often encountered, patients with FAD (defined as having a serum folic acid level ≤ 6 ng/mL in this study) sometimes show up at our clinic. In this study, 198 oral mucosal disease patients with FAD were enrolled from the oral mucosal disease clinic of National Taiwan University Hospital (NTUH). Their oral manifestations (including burning sensation and numbness of oral mucosa, dry mouth, dysfunction of taste), specific oral mucosal diseases (such as BMS, AG, RAU, and OLP), MCV, and blood levels of hemoglobin (Hb), iron, vitamin B12, folic acid, and homocysteine were inquired, examined, and recorded. These data were compared with the corresponding data of 198 age- and sex-matched healthy control participants without oral mucosal and systemic diseases to observe the frequencies of FAD in different types of patients with BMS, RAU, AG, or OLP and to assess whether FAD patients had higher frequencies of anemia, other hematinic deficiencies, abnormally high blood homocysteine level, high MCV (≥100 fL), low MCV (<80 fL), gastric parietal cell antibody (GPCA) positivity, and specific oral manifestations compared with healthy control participants.

Materials and methods

Patients

In this study, oral mucosal disease patients with FAD were defined as having a serum folic acid ≤ 6 ng/mL. This folic acid concentration was chosen because it was the cutoff point concentration for giving folic acid supplement treatment to FAD patients in our previous studies.15,16 Based on the above selected concentration for FAD, 198 oral mucosal disease patients (80 men and 118 women, age range 21–85 years, mean 54.5 ± 14.1 years) with FAD were recruited. For each patient, one age- (±2 years of each patient’s age) and sex-matched healthy control participant was selected. Thus, the normal control group consisted of 198 healthy control participants (80 men and 118 women, age range 20–84 years, mean 55.6 ± 13.6 years). All the patients and healthy control participants were seen consecutively, diagnosed, treated, and selected in the oral mucosal disease clinic of NTUH from July 2007 to March 2015. The 198 oral mucosal disease patients with FAD had one or two of the oral diseases including BMS, AG, RAU, and OLP. BMS was diagnosed when patients had a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.4,15 Patients were diagnosed as having partial or complete AG when their dorsal tongues showed partial or complete absence or flattening of filiform papillae, respectively.5,16 RAU was diagnosed when patients had at least one episode of oral ulcerations per month during the preceding years.1 OLP was diagnosed according to the following criteria: (1) a typical clinical presentation of radiating grayish-white Wickham striae or papules (nonerosive OLP) combined with erosion or ulceration on the bilateral buccal or vestibular mucosa (erosive OLP); and (2) biopsy specimens characteristic of OLP—that is, hyperkeratosis or parakeratosis, a slightly acanthotic epithelium with liquefaction degeneration of the basal epithelial cells, a pronounced band-like lymphocytic infiltrate in the lamina propria, and the absence of epithelial dysplasia.7,8 However, all FAD patients with areca quid chewing habit, autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren’s syndrome, pemphigus vulgaris, and cicatricial pemphigoid), inflammatory diseases, malignancy, or recent surgery were excluded. In addition, all FAD patients with serum creatinine concentrations indicative of renal dysfunction (i.e., men, >131 μM; women, >115 μM), and who reported a history of stroke, heavy alcohol use, or diseases of the liver, kidney, or coronary arteries were also excluded.17 Healthy control participants had either dental caries, pulpal disease, malocclusion, or missing teeth but did not have any oral mucosal or systemic diseases. None of our FAD patients had taken any prescription medication for malignancies, epilepsy, diabetes mellitus, infection, inflammation, BMS, AG, RAU, or OLP at least 3 months prior to entering the study.

According to the aforementioned diagnostic criteria, 198 oral mucosal disease patients with FAD retrieved from 77 of 847 BMS patients, 62 of 826 AG patients, 33 (8 also had AG and 4 also had BMS) of 306 RAU patients, and 26 (9 also had AG) of 336 OLP patients were included in this study. For all FAD patients and healthy control participants, oral manifestations including burning sensation and numbness of oral mucosa, dry mouth, dysfunction of taste, AG, RAU, and OLP were inquired, examined, and recorded. The blood samples were drawn from all patients and healthy control participants for measurement of complete blood count, blood iron, vitamin B12, folic acid, and homocysteine concentrations as well as serum GPCA levels. All patients and healthy control participants signed an informed consent form prior
to entering the study. This study was reviewed and approved by the Institutional Review Board at the NTUH.

**Determination of complete blood count and blood iron, vitamin B<sub>12</sub>, folic acid, and homocysteine concentrations**

The complete blood count and blood iron, vitamin B<sub>12</sub>, folic acid, and homocysteine concentrations were determined using routine tests performed in the Department of Laboratory Medicine of NTUH as described previously.<sup>4–16</sup>

**Determination of serum GPCA level**

The serum GPCA level was detected using the indirect immunofluorescence technique using rat stomach as a substrate as described previously.<sup>5,12</sup> In brief, 5-μm-thick cryostat sections of substrate tissues on slides were reacted with serially diluted patients’ and control participants’ sera in a moist chamber at room temperature for 30 minutes. The initial dilution of the patients’ and control participants’ sera was 1:20 with phosphate-buffered saline. After washing, the sections were incubated with fluorescein isothiocyanate-labeled goat antimouse 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 using an Olympus fluorescence microscope (Olympus, Tokyo, Japan). Sera were scored as positive when they produced fluorescence at a dilution of 20-fold or more.

**Statistical analysis**

Comparisons of the MCV and mean blood levels of Hb, iron, vitamin B<sub>12</sub>, folic acid, and homocysteine between 198 oral mucosal disease patients with FAD and 198 age- and sex-matched healthy control participants were performed using Student t test. The differences in frequency of Hb, iron, vitamin B<sub>12</sub>, or folic acid deficiency, of abnormally high blood homocysteine level, or of GPCA positivity between 198 FAD patients and 198 age- and sex-matched healthy control participants were compared using chi-square test. Comparisons of MCV, mean blood concentrations of Hb, iron, vitamin B<sub>12</sub>, folic acid, and homocysteine, and GPCA positivity between any two of the three groups of patients with macrocytic, normocytic, or microcytic RBCs were performed using Student t test or chi-square test, where appropriate. In addition, the differences in frequency of each oral manifestation between 198 oral mucosal disease patients with FAD and 198 age- and sex-matched healthy control participants were also compared using chi-square test. The result was considered to be significant if the p value was less than 0.05.

**Results**

The MCV and mean blood concentrations of Hb, iron, vitamin B<sub>12</sub>, folic acid, and homocysteine in 198 oral mucosal disease patients with FAD and in 198 age- and sex-matched healthy control participants 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 MCV (p < 0.001), Hb (for both men and women, both p < 0.001), iron (for both men and women; men, p = 0.008 and women, p = 0.005), vitamin B<sub>12</sub> (p = 0.005), and folic acid (p < 0.001) levels as well as significantly higher mean blood homocysteine level (p < 0.001) in oral mucosal disease patients with FAD than in healthy control participants (Table 1).

According to the World Health Organization (WHO) criteria, men with Hb < 13 g/dL and women with Hb < 12 g/dL were defined as having Hb deficiency or anemia.<sup>18</sup> Furthermore, patients with serum iron level < 60 μg/dL<sup>19</sup> or serum vitamin B<sub>12</sub> level < 200 pg/mL<sup>17</sup> were defined as having iron or vitamin B<sub>12</sub> deficiency, respectively. As stated before, patients with a serum folic acid level ≤6 ng/mL was defined as having FAD in this

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean corpuscular volume (MCV) and mean blood concentrations of hemoglobin (Hb), iron, vitamin B&lt;sub&gt;12&lt;/sub&gt;, folic acid, and homocysteine in 198 patients with folic acid deficiency (FAD; folic acid ≤ 6 ng/dL) and in 198 age- and sex-matched healthy control participants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>FAD patients (n = 198)</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>87.5 ± 9.3</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>58.6–136.8</td>
</tr>
<tr>
<td>Men (n = 80)</td>
<td>14.0 ± 1.5</td>
</tr>
<tr>
<td>Women (n = 118)</td>
<td>12.3 ± 1.5</td>
</tr>
<tr>
<td>Iron (μg/dL)</td>
<td>10.1–16.7</td>
</tr>
<tr>
<td>Men (n = 80)</td>
<td>93.9 ± 30.7</td>
</tr>
<tr>
<td>Women (n = 118)</td>
<td>84.7 ± 39.6</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; (pg/mL)</td>
<td>18.0–183.0</td>
</tr>
<tr>
<td>Folic acid (ng/mL)</td>
<td>47.3 ± 1.0</td>
</tr>
<tr>
<td>Homocysteine (μM)</td>
<td>11.6 ± 6.7</td>
</tr>
</tbody>
</table>

*Comparison of the MCV and mean blood levels of Hb, iron, vitamin B<sub>12</sub>, folic acid, and homocysteine between 198 FAD patients and 198 age- and sex-matched healthy control participants using Student t test with p < 0.01. SD = standard deviation.
study.\textsuperscript{15,16} Moreover, patients with blood homocysteine level > 12.8 \textmu M (which was the mean blood homocysteine level of healthy control participants plus 2 standard deviations) were defined as having abnormally high homocysteine level. Based on the above-mentioned definitions, 73 (36.9\%), 41 (20.7\%), and 10 (5.1\%) of 198 oral mucosal disease patients with FAD had concomitant Hb, iron, and vitamin B\textsubscript{12} deficiencies, respectively. Moreover, 64 (32.3\%) and 19 (9.6\%) of our 198 FAD patients had abnormally high blood homocysteine levels (> 12.8 \textmu M) and serum GPCA positivity, respectively (Table 2). However, none of the normal control participants were diagnosed as having Hb, iron, and vitamin B\textsubscript{12} deficiencies based on the aforementioned strict WHO criteria. However, FAD was found in 11 (5.6\%) of normal control participants. FAD patients had a significantly higher frequency of Hb, iron, vitamin B\textsubscript{12}, or folic acid deficiency, of abnormally high blood homocysteine level, and of GPCA positivity than healthy control participants (all \(p < 0.001\) except for vitamin B\textsubscript{12} deficiency, \(p = 0.004\)) (Table 2).

In this study, 73 (36.9\%) FAD patients were diagnosed as having anemia according to the WHO criteria.\textsuperscript{18} If macrocytic anemia due to FAD was defined as having an MCV \(\geq 100\) fL and folic acid \(\leq 6\) ng/mL; pernicious anemia as having MCV \(\geq 100\) fL, vitamin B\textsubscript{12} < 200 pg/mL, and serum GPCA positivity; iron deficiency anemia as having MCV < 80 fL and iron < 60 \mu g/dL; and thalassemia trait as having MCV < 74 fL, RBC count \(> 5.0 \times 10^{12}/L\), and Mentzer index (MCV/RBC) < 13, we found that of the 73 anemic FAD patients, three had macrocytic anemia due to FAD, one had pernicious anemia, 14 had iron deficiency anemia, eight had thalassemia trait, and the resting 47 patients had normocytic anemia.

When 198 FAD patients were further divided into Group 1 (8 patients with MCV \(\geq 100\) fL), Group 2 (159 patients with MCV between 80 and 99.9 fL), and Group 3 (31 patients with MCV < 80 fL), we found that Group 1 patients had significantly higher MCV (\(p < 0.001\)), higher mean serum iron level (for women only, \(p < 0.001\)), higher mean serum homocysteine level (\(p = 0.001\)), and higher frequency of serum GPCA positivity (\(p = 0.024\)) than Group 2 patients (Table 3). Moreover, Group 3 patients had a significantly lower mean Hb level (for men, \(p = 0.002\); for women, \(p < 0.001\)), lower MCV (\(p < 0.001\)), and lower mean serum iron level (for women only, \(p < 0.001\)) than Group 2 patients (Table 3). In addition, Group 1 patients had a significantly higher MCV (\(p < 0.001\)), higher mean serum iron level (for women only, \(p = 0.001\)), and higher mean serum homocysteine level (\(p = 0.041\)) than Group 3 patients (Table 3).

The oral manifestations in 198 oral mucosal disease patients with FAD and in 198 healthy control participants are shown in Table 4. We found that oral mucosal disease patients with FAD had significantly higher frequencies of all oral manifestations than healthy control patients (all \(p < 0.001\)), in which burning sensation of oral mucosa (72.2\%), AG (39.9\%), and dry mouth (35.4\%) were the three leading oral manifestations for FAD patients (Table 4).

### Discussion

This study found that of the 198 FAD patients, eight had macrocytic RBCs, 31 had microcytic RBCs, and 159 had normocytic RBCs. Moreover, 73 (36.9\%) of the 198 FAD patients had anemia (men with Hb < 13 g/dL and women with Hb < 12 g/dL). Of the 73 anemic FAD patients, four had macrocytic anemia (MCV \(\geq 100\) fL; including 3 with macrocytic anemia due to FAD and 1 with pernicious anemia), 22 had microcytic anemia (MCV < 80 fL; including 14 with iron deficiency anemia and 8 with thalassemia trait), and 47 had normocytic anemia (MCV between 80 fL and 99.9 fL). Of the 47 FAD patients with normocytic anemia, 10 had concomitant iron deficiency (iron < 60 \mu g/dL), 15 had concomitant relative iron deficiency (60 \mu g/dL < iron \leq 80 \mu g/dL), one had concomitant vitamin B\textsubscript{12} deficiency (vitamin B\textsubscript{12} < 200 pg/mL), and the resting 22 had FAD only. Because FAD may cause macrocytic anemia,\textsuperscript{19} but iron deficiency may cause microcytic anemia,\textsuperscript{19} those with both FAD and real or relative iron deficiency may have normocytic anemia because of the neutralization effect. Our findings indicate that FAD patients may have

### Table 2

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of participants (%)</th>
<th>(p) (Chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin deficiency (men, &lt; 13 g/dL; women, &lt; 12 g/dL)</td>
<td>73 (36.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Iron deficiency (&lt; 60 \mu g/dL)</td>
<td>41 (20.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vitamin B\textsubscript{12} deficiency (&lt; 200 pg/mL)</td>
<td>10 (5.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Folic acid deficiency (&lt; 6 ng/mL)</td>
<td>198 (100.0)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>High homocysteine level (&gt; 12.8 \textmu M)\textsuperscript{a}</td>
<td>64 (32.3)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>GPCA positivity</td>
<td>19 (9.6)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Comparison of frequency of hemoglobin, iron, vitamin B\textsubscript{12}, or folic acid deficiency, of abnormally high homocysteine level, or of serum GPCA positivity between 198 FAD patients and 198 age- and sex-matched healthy control subjects by chi-square test with \(p < 0.05\).

\textsuperscript{a} High homocysteine level was defined as patients with a homocysteine level greater than the mean of the homocysteine level of healthy control participants plus 2 standard deviations.
macrocytic (4.0%), normocytic (80.3%), or microcytic (15.7%) RBCs. Furthermore, in addition to macrocytic anemia (2.0%), FAD patients may have concomitant microcytic (11.1%) or normocytic (23.7%) anemia.

Of the 10 FAD patients with vitamin B12 deficiency, only four had serum GPCA positivity (i.e., the vitamin B12 deficiency can be attributed to the presence of GPCA). Thus, the vitamin B12 deficiency in the other six GPCA-negative FAD patients may be attributable to other causes including inadequate intake or malabsorption of vitamin B12, the presence of anti-intrinsic factor antibodies, or transcobalamin II deficiency.20

In this study, eight (4.0%) of 198 FAD patients had macrocytosis. Of the eight macrocytosis patients, two had concomitant vitamin B12 deficiency and GPCA positivity, one had concomitant iron deficiencies and GPCA positivity, one had concomitant iron deficiency, and the resting four had FAD only. Because vitamin B12 and/or folic acid deficiencies may result in the generation of macrocytic RBCs,17,18 the causes of macrocytosis in our eight FAD patients are probably due to vitamin B12 and/or folic acid deficiencies.19 Homocysteine is a sulfur-containing amino acid formed during methionine metabolism.21 Both vitamin B12 and folic

<table>
<thead>
<tr>
<th>Oral manifestation</th>
<th>FAD patients (n = 198)</th>
<th>Healthy control participants (n = 198)</th>
<th>p (Chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning sensation</td>
<td>143 (72.2)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Atrophic glossitis</td>
<td>79 (39.9)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>70 (35.4)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Numbness</td>
<td>49 (24.7)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Recurrent aphthous</td>
<td>33 (16.7)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ulcerations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral lichen planus</td>
<td>26 (13.1)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dysfunction of taste</td>
<td>23 (11.6)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Comparison of frequency of each oral manifestation between 198 FAD patients and 198 age- and sex-matched healthy control participants using chi-square test with p < 0.001.
acid act as coenzymes for the conversion of homocysteine to methionine. Higher blood homocysteine levels can cause oxidative stress, damage endothelium, and enhance thrombogenicity in experimental studies, and thus are associated with increased rates of coronary heart disease and stroke. Moreover, measurement of both serum methylmalonic acid and homocysteine levels is discovered to be a more sensitive method of screening for vitamin B12 deficiency (with a sensitivity of 99.8%) and thus can be used for detecting subclinical vitamin B12 deficiency. In this study, an abnormally higher blood homocysteine level was detected in 64 (32.3%) of the 198 FAD patients but could be found in only three (1.5%) of the 198 healthy control participants. The high blood homocysteine level in patients is found to be attributable to deficiencies in folic acid, vitamin B12, and vitamin B9, because a supplement therapy with folic acid, vitamin B12, and vitamin B9 to patients can reduce blood homocysteine levels. In this study, all 64 patients with abnormally higher blood homocysteine levels had FAD and nine FAD patients had concomitant vitamin B12 deficiency. Moreover, our FAD patients also had a significantly lower mean serum vitamin B12 or folic acid level compared with healthy control participants. Therefore, the high blood homocysteine level in our FAD patients was due to FAD or both folic acid and vitamin B12 deficiencies.

This study showed significantly higher frequencies of all oral manifestations in our oral mucosal disease patients with FAD than in healthy control participants (all \( p < 0.001 \)). These oral manifestations included burning sensation of oral mucosa (72.2%), AG (39.9%), dry mouth (35.4%), numbness of oral mucosa (24.7%), RAU (16.7%), OLP (13.1%), and dysfunction of taste (11.6%). Our previous studies found burning sensation of oral mucosa, dry mouth, numbness of oral mucosa, and dysfunction of taste in 100%, 75.7%, 43.9%, and 19.8% of 399 BMS patients, respectively; and in 100%, 79.0%, 57.4%, and 27.8% of 176 AG patients, respectively. Because 81, 79, 33, and 26 of our 198 FAD patients had concomitant BMS, AG, RAU, and OLP, this could explain why our oral mucosal disease patients with FAD had significantly higher frequencies of all oral manifestations including burning sensation of oral mucosa, dry mouth, numbness of oral mucosa, and dysfunction of taste than healthy control participants. In addition, 36.9% of our 198 FAD patients had anemia according to the WHO criteria. Anemia patients have reduced hemoglobin levels, which carries insufficient oxygen to oral mucosa, and finally results in atrophy of oral mucosa. Moreover, 20.7% and 32.3% of our 198 FAD patients had concomitant iron and vitamin B12 deficiencies, respectively. Iron is essential to the normal functioning of oral epithelial cells, and both vitamin B12 and folic acid play important roles in DNA synthesis and cell division. Oral epithelial cells have a high turnover rate. Therefore, deficiencies of iron, vitamin B12, and folic acid may result in oral epithelial atrophy. Furthermore, a high blood homocysteine level may result in an elevated frequency of thrombosis in the feeding arterioles that supply nutrients to the oral epithelial cells. This, in turn, leads to oral epithelial atrophy. Atrophic tongue dorsal or other oral mucosa in FAD patients could partially explain why a significant number of our oral mucosal disease patients with FAD had burning sensation and numbness of oral mucosa and dysfunction of taste. The reasons why BMS and AG patients may have burning sensation and numbness of oral mucosa, dry mouth, and dysfunction of taste compared with healthy control participants have been explained in detail in our previous studies.

Our results demonstrated that 36.9%, 20.7%, and 5.1% of our 198 oral mucosal disease patients with FAD had concomitant Hb, iron, and vitamin B12 deficiencies by WHO definitions, respectively. Moreover, 32.3% and 9.6% of our 198 FAD patients had abnormally high blood homocysteine levels and serum GPCA positivity, respectively. We also found a significantly higher frequency of Hb, iron, vitamin B12, or folic acid deficiency, of abnormally high blood homocysteine levels, or of GPCA positivity in our 198 FAD patients than in 198 healthy control participants. Of 73 anemic FAD patients, three had macrocytic anemia due to FAD, one had pernicious anemia, 14 had iron deficiency anemia, eight had thalassemia trait, and the resting 47 had normocytic anemia. Our findings indicate that, in addition to macrocytic anemia (2.0%), FAD patients may have concomitant normocytic (23.7%) or microcytic (11.1%) anemia.

References