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Original Article

Hemoglobin, iron, vitamin B12, and folic acid deficiencies and hyperhomocysteinemia in Behcet's disease patients with atrophic glossitis

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KEYWORDS
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Hyperhomocysteinemia

Background/Purpose: Behcet's disease (BD) patients should have recurrent aphthous stomatitis (RAS) but they may or may not have atrophic glossitis (AG). This study mainly assessed whether 30 AG-positive RAS/BD (AG^+RAS/BD) patients had significantly higher frequencies of hemoglobin, iron, vitamin B12, and folic acid deficiencies and of hyperhomocysteinemia than 33 AG-negative RAS/BD (AG^-RAS/BD) patients or 126 age- and sex-matched healthy control subjects.

Methods: The blood hemoglobin, iron, vitamin B12, folic acid, and homocysteine concentrations were measured and compared among 30 AG^+RAS/BD patients, 33 AG^-RAS/BD patients, and 126 healthy control subjects.

Results: We found that 43.3%, 33.3%, 13.3%, 6.7%, and 20.0% of 30 AG^+RAS/BD patients and 18.2%, 36.4%, 0%, 6.1%, and 9.1% of 33 AG^-RAS/BD patients had hemoglobin, iron, vitamin B12, and folic acid deficiencies and hyperhomocysteinemia, respectively. Moreover, 30 AG^+RAS/BD patients had significantly higher frequencies of hemoglobin, iron, vitamin B12, and folic acid deficiencies and of hyperhomocysteinemia than healthy control subjects (all *P*-values < 0.05), and had a higher frequency of hemoglobin deficiency ($P = 0.058$, marginal significance) and a significantly higher frequency of vitamin B12 deficiency ($P = 0.046$) than 33 AG^-RAS/BD patients. In addition, the 33 AG^-RAS/BD patients had significantly higher frequencies of hemoglobin and iron deficiencies than healthy control subjects (both *P*-values < 0.001).

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Conclusion: We conclude that AG$^+$RAS/BD patients do have significantly higher frequencies of hemoglobin, iron, vitamin B12, and folic acid deficiencies and of hyperhomocysteinemia than healthy control subjects and have significantly higher frequencies of hemoglobin and vitamin B12 deficiencies than AG$^-$RAS/BD patients.
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Introduction

Behcet's disease (BD) is a chronic, relapsing, multisystemic, and inflammatory disorder. It is defined as having recurrent aphthous stomatitis (RAS) plus two of the following conditions including recurrent genital ulcerations, eye lesions, skin lesions, and positive pathergy reaction according to the criteria for diagnosis of BD proposed by the International Study Group for BD.[1,2] The minor-typed RAS (minor RAS, 57%) is the most common type of RAS in BD patients, followed by the major-typed RAS (major RAS, 40%) and herpetiform-typed RAS (3%).[2]

BD appears to represent an abnormal immune process triggered by an infectious or environmental antigen in a genetically predisposed individual. The human leukocyte antigen B-51 (HLA-B51) has been discovered to be associated with BD.[2] Atrophic glossitic (AG) is a disease with multiple etiologies including deficiencies of riboflavin, niacin, vitamin B6, vitamin B12, folic acid or iron, diabetes mellitus, protein-calorie malnutrition, xerostomia, candidiasis, and *Helicobacter pylori* colonization.[3] BD patients are reported to have a relatively lower serum vitamin B12 or folate level and a higher frequency of vitamin B12 or folate deficiency than healthy control subjects.[4] Moreover, active, thrombotic or ocular BD patients have been found to have a significantly higher serum homocysteine level and a significantly higher frequency of hyperhomocysteinemia than healthy control subjects and than inactive, non-thrombotic or non-ocular BD patients, respectively.[5–12]

Our previous study found that a portion of AG and RAS patients do have hemoglobin (Hb), iron, vitamin B12, and folic acid deficiencies and hyperhomocysteinemia as well as significantly higher frequencies of Hb, iron, vitamin B12, and folic acid deficiencies and of hyperhomocysteinemia than healthy control subjects.[3,13] Hyperhomocysteinemia can be attributed to deficiencies of vitamin B6, vitamin B12, and/or folic acid.[14–16] Therefore, the concomitant presence of AG and RAS diseases in BD patients may influence the anemia status, hematinic deficiency, and hyperhomocysteinemia in BD patients.

In our oral mucosal disease clinic, patients with RAS, AG, burning mouth syndrome, oral lichen planus, or oral submucous fibrosis are frequently encountered.[3,13,15–37] For patients with these five specific diseases, complete blood count, serum iron, vitamin B12, folic acid, homocysteine, gastric parietal cell antibody (GPCA), thyroglobulin antibody (TGA), and thyroid microsomal antibody (TMA, also known as thyroid peroxidase antibody, TPO) levels are frequently examined to assess whether these patients have anemia, hematinic deficiencies, and serum GPCA, TGA, and TMA positivities.[3,13,15–37]

BD patients should have RAS (so-called RAS/BD patients in this study) but they may or may not have AG.[1,2] In this study, 63 RAS/BD patients including 30 AG-positive RAS/BD (AG$^+$RAS/BD) patients and 33 AG-negative RAS/BD (AG$^-$RAS/BD) patients were collected. We tried to assess whether 30 AG$^+$RAS/BD patients had significantly higher frequencies of Hb, iron, vitamin B12, and folic acid deficiencies and of hyperhomocysteinemia than 33 AG$^-$RAS/BD patients or 126 age- and sex-matched healthy control subjects. In addition, we also analyzed the anemia types in 13 anemic AG$^+$RAS/BD patients and 6 anemic AG$^-$RAS/BD patients.

Materials and methods

Subjects

The study group consisted of 63 BD patients (18 men and 45 women, age range 18–82 years, mean age 46 ± 16 years). For each BD patient, two age- (±2 years of each patient's age) and sex-matched healthy control subjects were selected. Thus, the normal control group consisted of 126 healthy control subjects (36 men and 90 women, age range 20–82 years, mean age 46 ± 13 years). All the patients and control subjects were seen consecutively, diagnosed, and treated in the Department of Dentistry, National Taiwan University Hospital from July 2007 to July 2017. Patients were diagnosed as having BD when they had RAS plus two of the following conditions including recurrent genital ulcers (on the scrotum and penile shaft of male patients or on the labia majora or labia minora of female patients), skin lesions (including erythema nodosum–like lesions, pseudofolliculitis, or papulopustular or acneiform lesions), and ocular lesions (including anterior or posterior uveitis, hypopyon, or retinal vasculitis) according to the criteria for diagnosis of BD proposed by the International Study Group for BD.[1,2] In this study, all the 63 BD patients had RAS that was characterized by the presence of at least one episode of oral ulcerations on the movable oral mucosa per month since childhood.[13,17–20] Moreover, partial or complete AG, which was defined as having partial or complete absence or flattering of filiform papillae on the dorsal surface of the tongue, respectively, was present in 30 RAS/BD patients (so-called AG$^+$RAS/BD patients).[3,15] The remaining 33 RAS/BD patients did not have concomitant partial or complete AG (so-called AG$^-$RAS/BD patients). Of the 63 BD patients, 57 also had skin lesions, 53 also had genital ulcers, 21 also had ocular lesions, and 9 also had arthritis or arthralgia affecting the knees, ankles, wrists, and elbows. BD patients with betel quid chewing habit, autoimmune diseases, or

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