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**Oral manifestations and blood profile in patients with iron
deficiency anemia**

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Abstract:

Iron deficiency anemia (IDA) is the most common type of anemia. This study evaluated whether IDA patients had specific oral manifestations and a particular blood profile compared to normal controls.

Introduction:

Iron deficiency anemia (IDA) is the most common type of anemia, with women being more frequently affected than men. It is estimated that 20% of women of childbearing age in the USA are iron-deficient due to the chronic blood loss associated with excessive menstrual flow. Moreover, 2% of adult men are iron-deficient because of chronic blood loss related to gastrointestinal diseases, such as peptic ulcer, diverticulosis, or malignancies.¹ In addition to chronic blood loss, an increased demand for red blood cell (RBC) production during pregnancy, a decreased intake of iron during infancy and old-age stage, and a reduced absorption of iron in patients with total gastrectomy are also possible causes of IDA.¹

Patients with IDA may have characteristic systemic symptoms such as fatigue, weakness, lightheadedness, shortness of breath, and palpitations. Oral symptoms and signs may include atrophic glossitis (AG), generalized oral mucosal atrophy, and tenderness or burning sensation of oral mucosa.¹ However, it is still not known whether IDA patients may have specific oral manifestations and what percentages of IDA patients may have these specific oral manifestations.

Materials and methods

Participants

The study group consisted of 75 IDA patients (11 men and 64 women, age range, 20–88 years, mean 51.7 ± 14.1 years). For each patient, two age- (± 2 years of each patient's age) and sex-matched healthy controls were selected. Thus, the normal control group consisted of 150 healthy individuals (22 men and 128 women, age range, 21–89 years, mean 52.4 ± 13.8 years). All the patients and controls were seen consecutively, diagnosed, treated, and selected in the oral mucosal disease clinic of NTUH from July 2007 to June 2013. Patients were diagnosed as having IDA when men had hemoglobin < 13 g/dL, women had hemoglobin < 12 g/dL, and all of them had serum iron level < 60 μ g/dL according to the World Health Organization criteria.^{2,3} Burning mouth syndrome (BMS) was diagnosed when patients had a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.^{4,5} Patients were diagnosed as having partial or complete AG when their dorsal tongues showed partial or complete absence or flattening of filiform papillae, respectively.^{5,6} RAU was diagnosed when patients had at least one episode of oral ulcerations per

month during the preceding years.⁷ 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.⁸⁻¹⁰ However, all IDA 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 IDA 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.¹¹ Healthy controls had either dental caries or mild periodontal diseases but did not have any oral mucosal or systemic diseases. None of our IDA patients had taken any prescription medication for BMS, AG, RAU or OLP at least 3 months prior to entering the study.

According to the aforementioned diagnostic criteria, the 75 IDA patients included 22 with OLP only, 19 with RAU only, 17 with AG only, 14 with BMS only, and three with both OLP and AG. For all IDA patients and healthy controls, oral manifestations including burning sensation and numbness of oral mucosa, dry mouth, dysfunction of taste, lingual varicosity, AG, RAU, and OLP were inquired, examined, and recorded. Blood samples were drawn from all patients and healthy controls for measurement of complete blood count, blood iron, vitamin B12, folic acid, and homocysteine concentrations. All patients and healthy controls signed informed consents prior to entering the study. This study was reviewed and approved by the Institutional Review Board at the NTUH.

Blood analysis

The complete blood count and blood iron, vitamin B12, folic acid, and homocysteine concentrations were determined by the routine tests performed in the Department of Laboratory Medicine of NTUH.

Statistical analysis

Comparisons of the mean RBC count, corpuscular cell volume (MCV), RBC distribution width (RDW), Mentzer index, and Green and King (G&K) index as well as mean blood levels of Hb, iron, total iron binding capacity (TIBC), vitamin B12, folic acid, and homocysteine between 75 IDA patients and 150 age- and sex-matched healthy controls were performed by Student *t* test. The differences in frequency of Hb, vitamin B12 or folic acid deficiency or of abnormally high blood homocysteine level between 75 IDA patients and 150 age- and sex-matched healthy controls were compared by Chi-square test. In addition, the differences in frequency of each oral manifestation between 75 IDA patients and 150 age- and sex- matched healthy controls

were also compared by Chi-square test. The result was considered to be significant if $p < 0.05$.

Results

The mean RBC count, MCV, RDW, Mentzer index, and G&K index as well as blood concentrations of Hb, iron, TIBC, vitamin B12, folic acid, and homocysteine in 75 IDA patients and in 150 age- and sex-matched healthy controls 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. IDA patients had significantly lower mean Hb level (for both men and women), RBC count, MCV, Mentzer index, iron level (for both men and women), and vitamin B12 level ($p < 0.001$ for all except $p = 0.003$ for vitamin B12) as well as significantly higher mean RDW, G&K index, and TIBC level ($p < 0.001$ for all) than healthy controls ([Table 1](#)). However, no significant difference in the mean blood folic acid or homocysteine level was discovered between 75 IDA patients and 150 healthy controls ([Table 1](#)). Previous studies suggested Mentzer index < 13 and G&K index < 65 as the criteria in differentiating β -thalassemia trait (β -TT) from pure IDA,¹²⁻¹⁸ i.e., β -TT patients usually have Mentzer index < 13 and G&K index < 65 , whereas IDA patient often have Mentzer index > 13 and G&K index > 65 . This study also found that all our 150 healthy controls and 75 IDA patients except one IDA patient had Mentzer index > 13 and G&K index > 65 .

Table 1. Mean red blood cell (RBC) count, mean corpuscular cell volume (MCV), RBC distribution width (RDW), Mentzer index, and Green and King (G&K) index as well as mean blood concentrations of hemoglobin (Hb), iron, total iron binding capacity (TIBC), vitamin B12, folic acid, and homocysteine in 75 patients with iron deficiency anemia (IDA) and in 150 age- and sex-matched healthy controls.

	Patients with IDA (n = 75)		Healthy controls (n = 150)		p (Student ttest)
	Mean \pm SD	Range	Mean \pm SD	Range	
Hb (g/dL)					
Men	10.6 \pm 1.9 (n = 11)	6.9– 12.7	15.1 \pm 0.7 (n = 22)	13.8– 16.3	<0.001*
Women	10.5 \pm 1.3 (n = 64)	7.1– 11.9	13.6 \pm 0.8 (n = 128)	12.2– 15.2	<0.001*
RBC ($\times 10^{12}/L$)	4.3 \pm 0.4	3.1–5.2	4.6 \pm 0.3	3.9–5.4	<0.001*
MCV (fl)	78.3 \pm 8.5	57.9– 103.8	90.9 \pm 3.2	82.4– 98.6	<0.001*
RDW (%)	15.8 \pm 2.4	12.1– 23.5	12.9 \pm 0.5	11.7– 14.8	<0.001*

	Patients with IDA (n = 75)		Healthy controls (n = 150)		p (Student ttest)
	Mean ± SD	Range	Mean ± SD	Range	
Mentzer index	18.4 ± 3.6	12.2-33.1	20.2 ± 1.6	16.0-25.1	<0.001*
G&K index	92.1 ± 16.8	57.2-145.2	77.8 ± 6.2	65.4-90.1	<0.001*
Iron (µg/dL)					
Men	30.4 ± 14.3 (n = 11)	10.0-55.0	99.0 ± 22.0 (n = 22)	69.0-149.0	<0.001*
Women	31.2 ± 13.4 (n = 64)	10.0-58.0	97.0 ± 27.0 (n = 128)	60.0-204.0	<0.001*
TIBC (µg/dL)	398.3 ± 67.6	207.0-527.0	307.9 ± 33.9	228.0-384.0	<0.001*
Vitamin B12 (pg/mL)	544.7 ± 278.9	150.0-1000.0	646.6 ± 211.1	259.0-1000.0	0.003
Folic acid (ng/mL)	13.0 ± 6.3	2.8-24.0	13.6 ± 5.7	4.1-24.0	0.473
Homocysteine (µM)	8.7 ± 5.0	3.6-39.9	8.1 ± 2.0	4.3-13.4	0.202

*Comparisons of the mean RBC count, MCV, RDW, Mentzer index, and G&K index as well as blood concentrations of Hb, iron, TIBC, vitamin B12, folic acid, and homocysteine between 75 IDA patients and 150 healthy controls by Student *t* test with $p < 0.05$.

Mentzer index = MCV / RBC ; G&K index = $MCV^2 \times RDW / (Hb \times 100)$.

According to the World Health Organization criteria, men with hemoglobin < 13 g/dL and women with hemoglobin < 12 g/dL were defined as having hemoglobin deficiency or anemia.² Furthermore, patients with serum iron level < 60 µg/dL,³ serum vitamin B12 level < 200 pg/mL (148 pmol/L),¹¹ or folic acid level < 4 ng/mL (10 nM)¹⁹ were defined as having iron, vitamin B12, or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level > 12.1 µmol/L (which was the mean blood homocysteine level of healthy controls plus two standard deviations) were defined as having abnormally high homocysteine level. By the above-mentioned definitions, 75 (100%), six (8.0%), and two (2.7%) of 75 IDA patients had Hb, vitamin B12, and folic acid deficiencies, respectively. However, none of the normal controls was diagnosed as having Hb, vitamin B12, or folic acid deficiencies by the aforementioned strict World Health Organization criteria. Thus, IDA patients had a significantly higher frequency of Hb ($p < 0.001$) and vitamin B12 deficiencies ($p = 0.002$) than healthy controls. In addition, 10 (13.3%) IDA patients and three (2.0%) normal controls had an abnormally high blood

homocysteine level. Thus, there was also a significant difference in blood homocysteine level between IDA patients and normal controls ($p = 0.002$). The oral manifestations in 75 IDA patients and in 150 healthy controls are shown in [Table 2](#). IDA patients had significantly higher frequencies of all oral manifestations than healthy controls ($p < 0.001$ for all), in which burning sensation of oral mucosa (76.0%), lingual varicosity (56.0%), dry mouth (49.3%), oral lichen planus (33.3%), and atrophic glossitis (26.7%) were the five leading oral manifestations for IDA patients ([Table 2](#)).

Table 2. Oral manifestations in 75 patients with iron deficiency anemia and in 150 age- and sex-matched healthy controls.

Oral manifestation	Participant number (%)		p (Chi-square test)
	Patients with iron deficiency anemia ($n = 75$)	Healthy controls ($n = 150$)	
Burning sensation	57 (76.0)	0 (0)	<0.001*
Lingual varicosity	42 (56.0)	0 (0)	<0.001*
Dry mouth	37 (49.3)	0 (0)	<0.001*
Oral lichen planus	25 (33.3)	0 (0)	<0.001*
Atrophic glossitis	20 (26.7)	0 (0)	<0.001*
Recurrent aphthous ulcerations	19 (25.3)	0 (0)	<0.001*
Numbness	16 (21.3)	0 (0)	<0.001*
Dysfunction of taste	9 (12.0)	0 (0)	<0.001*

*Comparison of frequency of each oral manifestation between 75 patients with iron deficiency anemia and 150 age- and sex-matched healthy controls by Chi-square test with $p < 0.05$.

develops on the skin. The rash usually starts on the forehead or beside the ears. It then spreads over the face, travels downwards over the trunk and arms, and finally spreads over the lower body, A measles rash lasts for about five or six days and then disappears(*1)

2-Rubella is generally a milder disease than measles and usually produces no complications, It may even be a subclinical infection (one that doesn't

Discussion

This study showed significantly higher frequencies of all oral manifestations in IDA patients than in healthy controls ($p < 0.001$). These

oral manifestations included burning sensation of oral mucosa (76.0%), lingual varicosity (56.0%), dry mouth (49.3%), OLP (33.3%), AG (26.7%), RAU (25.3%), numbness of oral mucosa (21.3%), and dysfunction of taste (12.0%). Our previous studies found burning sensation of oral mucosa, lingual varicosity, dry mouth, numbness of oral mucosa, and dysfunction of taste in 100%, 92.5%, 75.7%, 43.9%, and 19.8% of 399 BMS patients, respectively,⁴ and in 100%, 98.9%, 79.0%, 57.4%, and 27.8% of 176 AG patients, respectively.⁶ Because 33.3%, 26.7%, 25.3%, and 18.7% of our 75 IDA patients had concomitant OLP, AG, RAU, and BMS, respectively, this could explain why our IDA patients had significantly higher frequencies of all oral manifestations including burning sensation of oral mucosa, lingual varicosity, dry mouth, numbness of oral mucosa, and dysfunction of taste than healthy controls. In addition, all (100%) of our 75 IDA patients had anemia according to the World Health Organization criteria.² Anemia patients have reduced hemoglobin levels and so carry insufficient oxygen to oral mucosa and finally results in atrophy of oral mucosa.¹ Iron deficiency may also lead to atrophy of oral mucosa, because iron is essential to the normal functioning of oral epithelial cells and in an iron deficiency state oral epithelial cells turn over more rapidly and produce an atrophic or immature mucosa.¹ Atrophic oral mucosa in IDA patients could partially explain why a significant number of our IDA patients 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, lingual varicosity, dry mouth, and dysfunction of taste than healthy controls have been explained in detail in our previous papers.^{4,6}

This study also found that IDA patients had significantly lower mean Hb level, RBC count, MCV, Mentzer index, iron level, and vitamin B12 level as well as significantly higher mean RDW, G&K index, and TIBC level than healthy controls. IDA patients had severe iron deficiency, which leads to a significantly reduced production of Hb and RBC, and also results in the generation of microcytic RBC in IDA patients.¹²⁻¹⁸ Moreover, some of our IDA patients also had vitamin B12 or folic acid deficiency, which is a condition that can lead to production of macrocytic RBC. Because small-, normal-, and large-sized RBCs were produced in one individual in some of our IDA patients, these finally resulted in an elevated mean RDW in our IDA patients. Although IDA patients had significant iron deficiency, the bone marrow hematopoietic function of IDA patients may be nearly normal; this

thus leads to a slightly and significantly lower mean RBC count in IDA patients.¹²⁻¹⁸ In addition, a significant iron deficiency may result in a significantly elevated TIBC level in our IDA patients compared to healthy controls.

β -TT and pure IDA patients usually have microcytic and hypochromic anemia. To date, more than 10 discrimination indices have been reported using RBC indices obtained by automated blood count to distinguish β -TT from pure IDA.¹²⁻¹⁸ Several authors have calculated the sensitivity and specificity of these discrimination indices in differentiating β -TT from pure IDA. However, none of these indices has a sensitivity and specificity of 100% in prediction of β -TT and pure IDA.¹²⁻¹⁸ Among these discrimination indices, most previous investigators agree that the majority of β -TT patients have Mentzer index < 13 and G&K index < 65, whereas the majority of pure IDA patients have Mentzer index > 13 and G&K index > 65. These two indices are used because the Mentzer index was the first proposed index that is relatively reliable and very easy to calculate (MCV/RBC)¹² and the G&K index has been reported to provide the highest reliabilities in differentiating β -TT from pure IDA with the sensitivity of 85.0% and the specificity of 94.8% in Chinese children¹⁸ and the sensitivity of 84.8% and the specificity of 83.8% in the Palestinian population.¹⁶ In our previous study, all our β -TT patients had Mentzer index < 13 and G&K index < 65.⁵ In this study, all healthy controls and IDA patients except one IDA patient had Mentzer index > 13 and G&K index > 65. These findings indicate that both the Mentzer and G&K indices are good discrimination indices for differentiating β -TT from IDA or normal status.

Our results show significantly higher frequencies of all oral manifestations in IDA patients than in healthy controls, with a burning sensation of oral mucosa, lingual varicosity, dry mouth, OLP, and AG being the five leading oral manifestations for IDA patients. We also found that IDA patients had significantly lower mean Hb level, RBC count, MCV, Mentzer index, iron level, and vitamin B12 level as well as significantly higher mean RDW, G&K index, and TIBC than healthy controls. We conclude that IDA patients have specific oral manifestations and a particular blood profile compared to normal controls.

Conclusion

IDA patients have specific oral manifestations and a particular blood profile compared to normal controls.

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