Original Article

Oral manifestations and blood profile in patients with thalassemia trait

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Received 31 August 2013; accepted 21 September 2013

**KEYWORDS**
burning sensation; Green and King index; hemoglobin; mean corpuscular volume; Mentzer index; oral manifestation

**Background/Purpose:** Patients with thalassemia trait (TT) may have anemia. This study evaluated whether TT patients had specific oral manifestations and a particular blood profile compared with normal individuals.

**Methods:** The oral manifestations and mean red blood cell count, corpuscular cell volume, red blood cell distribution width, Mentzer index, and Green and King index as well as blood concentrations of hemoglobin, iron, total iron binding capacity, vitamin B12, folic acid, and homocysteine in 65 TT patients and in 130 age- and sex-matched healthy controls were measured and compared.

**Results:** TT patients had significantly higher frequencies of all oral manifestations than healthy controls (p < 0.001 for all), in which burning sensation of oral mucosa (90.8%), lingual varicosity (90.8%), dry mouth (72.3%), atrophic glossitis (32.3%), and numbness of the oral mucosa (30.8%) were the five leading oral manifestations for TT patients. Moreover, TT patients had significantly lower mean hemoglobin level, corpuscular cell volume, Mentzer index, and Green and King index (p < 0.001 for all) as well as significantly higher mean red blood cell count and red blood cell distribution width (p < 0.001 for both) than healthy controls. However, no significant difference in the mean blood iron, total iron binding capacity, vitamin B12, folic acid, or homocysteine levels was discovered between 65 TT patients and 130 healthy controls.

**Conclusion:** TT patients have specific oral manifestations and a particular blood profile compared to normal individuals.

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Introduction

Thalassemia is an autosomal recessive blood disorder in which the body makes an abnormal form of hemoglobin (Hb). Hb is composed of four protein chains, two α and two β globin chains arranged into a heterotetramer. The α globin chains are encoded by two closely linked genes on chromosome 16 and the β globin chains are encoded by a single gene on chromosome 11. There are two main types of thalassemia: α-thalassemia occurs when a gene or genes related to the α globin protein are missing or mutated, and β-thalassemia occurs when similar gene defects affect production of the β globin protein. Both α- and β-thalassemias include the following forms: thalassemia major (with the defective genes from both parents); and thalassemia minor (with the defective gene from only one parent). The most severe form of α-thalassemia major causes stillbirth. Children born with thalassemia major may be normal at birth, but develop severe anemia during the first year of life. Other symptoms and signs include bone deformities in the face, fatigue, growth failure, shortness of breath, and yellow skin (jaundice). Patients with the minor form of α- or β-thalassemia often have hypochromic and microcytic anemia, but usually have no apparent systemic symptoms.1

Hb is the protein in red blood cells (RBCs) that carries oxygen. People with thalassemia make more abnormal forms of α-globin chain, β-globin chain, and Hb compared to normal individuals. Imbalances of globin chains cause hemolysis, which results in mild to severe anemia.1 Patients with anemia may have atrophic glossitis (AG) or generalized oral mucosal atrophy and tenderness or burning sensation of oral mucosa.2 However, it is still not known whether patients with thalassemia trait (TT including α- or β-thalassemia minor) may have specific oral manifestations and what percentages of TT patients may have the oral manifestations. In this study, 65 TT patients were collected 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, lingual varicosity, AG, recurrent aphthous ulcerations (RAU), and oral lichen planus (OLP)], complete blood count, and blood chemistry (including blood levels of Hb, iron, vitamin B12, folic acid, and homocysteine) were inquired, examined, and recorded. These data were compared with corresponding data in 130 age- and sex-matched healthy controls without oral mucosal and systemic diseases to assess whether TT patients had higher frequencies of specific oral manifestations and a particular blood profile compared to healthy controls.

Materials and methods

Participants

The study group consisted of 65 TT patients (14 men and 51 women; age range 20–88 years, mean 56.2 ± 14.4 years). For each patient, two age- (±2 years of each patient’s age) and sex-matched healthy control individuals were selected. Thus, the normal control group consisted of 130 healthy participants (28 men and 102 women, age range 21–89 years, mean 55.1 ± 14.4 years). All patients and healthy 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 TT when they had RBC count >5.0 × 10¹²/L,1 mean corpuscular volume (MCV) <74 fl,4 Mentzer index (MCV/RBC) <13,5 and Green and King (G&K) index [MCV² × RDW/(Hb × 100)] <65.6 Burning mouth syndrome (BMS) was diagnosed when patients had a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations.7 Patients were diagnosed as having partial or complete AG when their dorsal tongues showed partial or complete absence or flattening of filiform papillae, respectively.8 RAU was diagnosed when patients had at least one episode of oral ulcerations per month during the preceding years.9 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 or EOLP); 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.10–12 However, all TT patients with areca quid chewing habit, autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, pemphigus vulgaris, and cicatricial pemphigoid), inflammatory diseases, malignancy, or recent surgery were excluded. In addition, all TT 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.13 Healthy controls had either dental caries or mild periodontal diseases but did not have any oral mucosal or systemic diseases. None of our TT patients had taken any prescription medication for BMS, AG, RAU, or OLP for at least 3 months before entering the study.

According to the aforementioned diagnostic criteria, the 65 TT patients included 31 (4 men and 27 women; mean age, 54.0 years) with BMS, 19 (4 men and 15 women; mean age, 61.8 years) with AG, seven (3 men and 4 women; mean age, 50.4 years) with EOLP, six (2 men and 4 women; mean age, 55.9 years) with RAU, and two (1 man and 1 woman; mean age, 58 years) with both RAU and AG. For all TT 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. The 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 consent before 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 B12, folic acid and homocysteine concentrations

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, MCV, RDW, Mentzer index, and G&K index as well as mean blood concentrations of Hb, iron, TIBC, vitamin B12, folic acid, and homocysteine were performed by Student t test. The differences in frequency of hemoglobin deficiency or of abnormally high blood homocysteine level between 65 TT patients and 130 healthy controls were compared by Chi-square test. In addition, the difference in frequency of each oral manifestation between 65 TT patients and 130 age- and sex-matched healthy controls were compared by Fisher exact test. The result was considered to be significant if the p-value was <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 65 TT patients and in 130 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. We found that TT patients had significantly lower mean Hb level (p < 0.001 for both men and women), MCV (p < 0.001), Mentzer index (p < 0.001), and G&K index (p < 0.001) as well as significantly higher mean RBC count (p < 0.001) and RDW (p < 0.001) than healthy controls (Table 1). However, no significant difference in the mean blood iron, TIBC, vitamin B12, folic acid, or homocysteine level was discovered between 65 TT patients and 130 healthy controls (Table 1).

According to the World Health Organization criteria, men with hemoglobin <13 g/dL and women with hemoglobin <12 g/dL are defined as having hemoglobin deficiency or anemia. Furthermore, patients with serum iron level <60 μg/dL, serum vitamin B12 level <200 pg/mL (148 pm), or folic acid level <4 ng/mL (10 nm) are defined as having iron, vitamin B12, or folic acid deficiency, respectively. In addition, patients with the blood homocysteine level >12.4 μM (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, 32 (49.2%, 5 men and 27 women) of 65 TT patients and none of the normal controls were diagnosed as having Hb deficiency or anemia. Thus, TT patients had a significantly higher frequency of Hb deficiency than healthy controls (p < 0.001). However, none of TT patients or normal controls were diagnosed as having iron, vitamin B12 and folic acid deficiencies by the aforementioned strict World Health Organization criteria. In addition, 6 (9.2%) TT patients and 3 (2.3%) normal controls had abnormally high blood homocysteine levels.

Table 1  The mean ± standard deviation (SD) red blood cell (RBC) count, mean corpuscular cell volume (MCV), red blood cell 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 65 patients with thalassemic trait (TT) and in 130 age- and sex-matched healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients with thalassemic trait (n = 65)</th>
<th>Healthy controls (n = 130)</th>
<th>p Student t test</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>12.7 ± 1.3 (n = 14)</td>
<td>9.3–13.9</td>
<td>15.1 ± 0.6 (n = 28)</td>
</tr>
<tr>
<td>Women</td>
<td>11.7 ± 0.8 (n = 51)</td>
<td>9.5–13.3</td>
<td>13.6 ± 0.7 (n = 102)</td>
</tr>
<tr>
<td>RBC (×10¹²/L)</td>
<td>5.8 ± 0.4</td>
<td>5.1–6.9</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>66.1 ± 3.5</td>
<td>57.9–72.7</td>
<td>90.9 ± 3.3</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>15.5 ± 0.8</td>
<td>13.6–18.0</td>
<td>12.9 ± 0.6</td>
</tr>
<tr>
<td>Mentzer index</td>
<td>11.5 ± 1.0</td>
<td>9.4–12.9</td>
<td>19.8 ± 1.9</td>
</tr>
<tr>
<td>G&amp;K index</td>
<td>56.8 ± 5.1</td>
<td>45.6–64.7</td>
<td>77.5 ± 6.4</td>
</tr>
<tr>
<td>Iron (μg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>98.9 ± 25.6 (n = 14)</td>
<td>65.0–160.0</td>
<td>99.4 ± 23.7 (n = 28)</td>
</tr>
<tr>
<td>Women</td>
<td>96.8 ± 24.0 (n = 51)</td>
<td>60.0–140.0</td>
<td>96.2 ± 26.1 (n = 102)</td>
</tr>
<tr>
<td>TIBC (μg/dL)</td>
<td>301.2 ± 35.6</td>
<td>203.0–407.0</td>
<td>307.0 ± 32.6</td>
</tr>
<tr>
<td>Vitamin B12 (pg/mL)</td>
<td>654.9 ± 255.6</td>
<td>250.0–1000.0</td>
<td>655.4 ± 220.9</td>
</tr>
<tr>
<td>Folic acid (ng/mL)</td>
<td>13.6 ± 6.8</td>
<td>4.5–24.0</td>
<td>13.6 ± 5.6</td>
</tr>
<tr>
<td>Homocysteine (μM)</td>
<td>8.7 ± 2.5</td>
<td>4.5–16.2</td>
<td>8.4 ± 2.0</td>
</tr>
</tbody>
</table>

*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 65 TT patients and 130 healthy controls by Student t test with p < 0.05. Mentzer index = MCV / RBC; G&K index = MCV² × RDW/(Hb × 100).
homocysteine level. Thus, there was no significant difference in blood homocysteine level between TT patients and normal controls ($p = 0.07$).

The oral manifestations in 65 TT patients and in 130 healthy controls are shown in Table 2. TT patients had significantly higher frequencies of all oral manifestations than healthy controls ($p < 0.001$ for all), in which burning sensation of oral mucosa (90.8%), lingual varicosity (90.8%), dry mouth (72.3%), atrophic glossitis (32.3%), and numbness of the oral mucosa (30.8%) were the five leading oral manifestations for TT patients (Table 2).

### Discussion

This study showed significantly higher frequencies of all oral manifestations in TT patients than in healthy controls ($p < 0.001$ for all). These oral manifestations included burning sensation of oral mucosa (90.8%), lingual varicosity (90.8%), dry mouth (72.3%), AG (32.3%), numbness of oral mucosa (30.8%), dysfunction of taste (20.0%), RAU (12.3%), and EOLP (10.8%). 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, and in 100%, 98.9%, 79.0%, 57.4%, and 27.8% of 176 AG patients, respectively. Because 47.6%, 32.3%, 12.3%, and 10.8% of our TT patients had concomitant BMS, AG, RAU and EOLP, this could explain why our TT 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, 32 (49.2%) of our 65 TT patients had anemia. Anemia patients have reduced hemoglobin levels, which carry insufficient oxygen to oral mucosa and finally results in atrophy of oral mucosa. The atrophic oral mucosa could also partially explain why a significant number of TT patients had burning sensation and numbness of oral mucosa and dysfunction of taste. The reasons for BMS and AG patients having burning sensation and numbness of oral mucosa, lingual varicosity, dry mouth, and dysfunction of taste than healthy controls may have been explained in detail in our previous papers.

This study also found that TT patients had significantly lower mean Hb level, MCV, Mentzer index, and G&K index as well as significantly higher mean RBC count and RDW than healthy controls. TT patients make abnormal α and β globin chains, which are easily destructed, resulting in a significantly reduced Hb level and MCV in TT patients. Moreover, Hb is a heterotetramer composed of two α and two β globin chains. A TT patient usually carries an abnormal form of either α or β globin chain. Different combinations and quantities of normal and abnormal α and β globin chains in different RBCs finally result in an elevated mean RDW in TT patients. However, the bone marrow hematopoietic function of TT patients may be nearly normal; this thus leads to compensatory production of many hypochromic and microcytic RBCs resulting in a significantly higher mean RBC count in TT patients.

Microcytic RBCs in TT patients was not due to iron deficiency, because there was no significant iron deficiency in our TT patients compared to healthy controls.

DNA sequencing of α and β globin chain genes to assess whether there is presence of gene mutation or missing is the most reliable method to diagnose both α- and β-thalassemias. However, DNA sequencing of α and β globin chain genes needs a relatively long period of time. β-TT can also be confirmed when patients have the HbA2 level >3.5% and normal serum ferritin level. Nevertheless, determination of HbA2 and serum ferritin levels is also time-consuming. To date, >10 discrimination indices have been reported using RBC indices obtained by automated blood count. Several authors calculated sensitivity and specificity of these discrimination indices in differentiating TT from iron deficiency anemia. However, none of these indices has a sensitivity and specificity of 100% in prediction of TT and iron deficiency anemia. This study adopted the simple factors such as RBC count $>5 \times 10^{12}$/L, MCV $<74 \text{ fL}$, Mentzer index $<13$, and G&K index $<65$ to help confirm the diagnosis of α- or β-TT. The latter two indices were used because the Mentzer index was the first proposed index, which was relatively reliable and very easy to calculate (MCV/RBC) and the G&K index has been reported to provide the highest reliabilities in differentiating β-TT from iron deficiency anemia with the sensitivity of 85.0% and specificity of 94.8% in Chinese children and the

### Table 2

<table>
<thead>
<tr>
<th>Oral manifestation</th>
<th>Participant number (%)</th>
<th>Healthy controls</th>
<th>$p$ (Chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning sensation</td>
<td>59 (90.8)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Lingual varicosity</td>
<td>59 (90.8)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>47 (72.3)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Atrophic glossitis</td>
<td>21 (32.3)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Numbness</td>
<td>20 (30.8)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Dysfunction of taste</td>
<td>13 (20.0)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Recurrent aphthous ulcerations</td>
<td>8 (12.3)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
<tr>
<td>Oral lichen planus</td>
<td>7 (10.8)</td>
<td>0 (0)</td>
<td>$&lt;0.001^*$</td>
</tr>
</tbody>
</table>

*Comparison of frequency of each oral manifestation between 65 patients with thalassemia trait and 130 age- and sex-matched healthy control individuals by Chi-square test with $p < 0.05$. 

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74 fL, Mentzer index $<13$, and G&K index $<65$ to help confirm the diagnosis of α- or β-TT. The latter two indices were used because the Mentzer index was the first proposed index, which was relatively reliable and very easy to calculate (MCV/RBC) and the G&K index has been reported to provide the highest reliabilities in differentiating β-TT from iron deficiency anemia with the sensitivity of 85.0% and specificity of 94.8% in Chinese children and the
sensitivity of 84.8% and specificity of 83.8% in Palestinian population.\textsuperscript{18} The accurate diagnosis rate should be very high, because this study used four criteria to select TT patients. In addition, the more criteria used, the higher the accurate diagnosis rate.

The major problem of TT patients is the gene defect that results in synthesis of abnormal forms of \(\alpha\) or \(\beta\) globin chain and Hb.$^1$ Compared to healthy controls, TT patients usually do not have higher frequencies of gastrointestinal defects or the presence of gastric parietal cell autoantibodies resulting in malabsorption of iron, vitamin B12 and folic acid.\textsuperscript{17–21} This could explain why there was no significant difference in the mean blood iron, vitamin B12, folic acid, or homocysteine levels between the 65 TT patients and 130 healthy controls in this study.

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

References