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Prevalence of autoimmune thyroid disease in recurrent aphthous stomatitis

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ABSTRACT

Introduction: Recurrent aphthous stomatitis (RAS) is a multifactorial recurrent oral lesion; which is an autoimmune disease. TH1 cytokines are the most important etiological factors. Autoimmune thyroid disease (ATD) is one of the most common autoimmune diseases and generally coexists with other autoimmune diseases. This study assessed the prevalence of thyroid disease in patients with recurrent aphthous stomatitis.

Materials and Methods: This case control study assessed 100 patients with RAS. Oral medicine specialists diagnosed RAS clinically; venous blood samples were analyzed for thyroid stimulating hormone (TSH), free triiodothyronine (fT3), total thyroxine (fT4), thyroglobulin, anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin antibody (anti-TG) levels.

Results: Fifty patients with RAS aged between 18-42 years (28.5±5.8) and 50 healthy volunteers aged 19-45 years (27.3±5.4) participated. In RAS patients, fT3 and TSH levels were significantly higher (P=0.031, P=0.706); however, fT4 level was lower in the RAS group (P=0.447). Anti TG and anti-TPO levels were significantly higher in the RAS group (P=0.008, P=0.067).

Conclusion: Our study showed that ATD prevalence was significantly higher in RAS patients. Based on this study, we recommend assessment of thyroid hormones and antibodies in RAS patients.

Keywords: Recurrent aphthous stomatitis; Thyroid autoimmune disease; Thyroid hormone, Thyroid antibodies.

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common recurrent painful oral ulcers clinically diagnosed by multiple round symmetrical ulcers with a red halo [1,2]. It is categorized as minor, major or herpetiform [3,4]. The prevalence is variable ranging from 2% to 66%. RAS apparently begins between the ages of 10 to 19 years, and its incidence decreases with age [5]; 39% of children whose parents have RAS have the same

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Treatment is supportive; corticosteroids and immunosuppressive agents are known to affect RAS [1,3]. Although the main etiology is unclear, it is obvious that it is multifactorial; thus many factors such as trauma, hormonal changes, food and vitamin deficiencies, genetics and stress can cause RAS through immunologic dysregulation [9]. Many studies have revealed the role of immunologic changes in RAS and some of them show that RAS can be an autoimmune disease [9]. The thyroid gland is one of the most common autoimmune targets; it can be affected simultaneously with other autoimmune organ involvements. Autoimmune thyroid disease (ATD) can be detected via antibodies against the thyroglobulin, thyroid peroxidase or thyrotropin receptor autoantigens [10].

Materials and Methods

We assessed 100 patients in this descriptive case control study from September to October 2013; 50 patients (28 females, 22 males) who were clinically diagnosed with RAS by an oral medicine specialist and 50 (33 females, 17 males) healthy volunteers were included. The inclusion criteria were as follows:

- At least three bouts of RAS in a year.
- No intake of vitamins, minerals or food supplements within the last 3 months.
- No pregnancy or nursing.
- No history of systemic disease, (gastrointestinal, immunologic, or endocrine).
- No history of thyroid treatment.

Free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) via ELISA (ELISA Reader Hyperion, Germany), anti-thyroglobulin (AbTG) via ELISA (DiaMetra, Germany) and anti-thyroid peroxidase antibodies (Ab-TPO) via ELISA (Monobind Inc., USA) were measured for each subject. The normal ranges for thyroid hormones and autoantibodies were accepted as follows: FT3: 1.9–4.3 pg⁄mL, FT4: 0.70–1.8 ng⁄dL, TSH:0.32–5.2 mlu/L, AbTG:>4 elevated, <4 normal Au/Ml and AbTPO: >40 positive, <40 negative Iu/mL.

Results

RAS group included 50 patients (28 females and 22 males) aged 18-42 years (28.5. Control group included 50 patients (33 females and 17 males) aged 19-45 years (27.3. The mean age and gender distribution were similar between the two groups (Table 1). Hematologic findings were analyzed and there were no significant differences between the two groups (Table 2). The ranges of thyroid hormone and autoantibody levels of the patient and control groups are displayed in Table 3. The FT3 level (3.045±1.20) was significantly higher in the RAS group (P=0.031) but TSH level (1.398±1.24) was not significantly higher in the RAS group (P=0.706).

FT4 value in the patient group (1.623±0.465) was lower than that in the control group (1.889±0.419) and there was no statistically significant difference between the two groups (P=0.447). TSH levels in the patient group (1.398±1.24) were higher than in the control group (1.178±1.14) and there was no statistically significant difference between the two groups (P=0.706). Anti-TG level was 7.772±21.90 in the patient group and 2.919±8.28 in the control group and the difference in this respect between the two groups was statistically significant (P=0.008). Anti-TPO level in the patient group (57.695±129.73) was higher than that in the control group (34.489±105.26) , but there was no statistically significant differences between the two groups in this regard (P=0.067). Anti-TG was positive in the RAS group (7.772 ± 21.90) but it was within the normal range in the control group (2.919±8.28).

The Anti-TPO level was positive in the patient group (57.695±129.73) and negative (34.489±105.26) in the control group. The prevalence rates of thyroid autoantibodies in the study group are listed in Table 3. In RAS group, we had 9 (18%) patients, with high levels of anti–TPO, 12 (24%) patients with high levels of anti-TG and 6 (21%) patients with high levels

of both. In the control group 6 (12%) had a high level of anti-TPO, 4 (8%) had a high level of anti-TG and 1 (2%) had high levels of both. Thyroid hormone levels, thyroid disorders, autoimmune conditions and normal groups are shown in Table 4. In regard to thyroid disorder diagnosis in both RAS and healthy groups, 45 (90%) persons were diagnosed as euthyroid.

One (2%) patient in RAS group was hypothyroid and 3 (6%) patients in RAS group, and 4 patients (8%) in the control healthy group were hyperthyroid subclinically; 1 (2%) patient of both groups was clinically hyperthyroid. The mean FT3 in the patient group and the control group was 2.782±0.71 and 3.045±1.20, respectively. The mean FT4 in the patient group and the control group was 1.623±0.465 and 1.889±0.419, respectively. The mean TSH in the patient group and the control group was 1.398±1.24 and 1.178±1.14, respectively.

Discussion

Despite the multifactorial nature of the pathogenesis of RAS, most studies have shown the role of autoimmunity in the pathogenesis of RAS. Many studies have reported increased levels of TNFα, IL2 and IFNγ and decreased level of IL4, [5,10]. Cytokines such as IL and TNFα are produced by keratinocytes and activate T cells [11,12] High levels of IL2, TNFα and INFγ have been reported due to autoimmune thyroiditis. Th1 cytokines can be the most common immunologic factor for RAS and ATD [13,14]. ATD is one of the most common endocrine pathologies which can be diagnosed by anti-TPO and anti-TG as the first markers [9].

The prevalence of anti-TPO is 6-11% and is higher in females. Concomitantly high levels of anti-TPO and anti-TG are important. Presence of anti-TPO in euthyroid patients is a risk factor of ATD in 2% of the population [15]. Hypothyroidism is more common but hyperthyroidism can occur after years. In this study, we had significantly higher levels of thyroid antibodies in the RAS group, because the samples were taken in an active period of RAS; the mean age of our patients was higher than other studies. Most of the patients in our study were hypothyroid. Autoimmune thyroid diseases were higher in the RAS group; which is different from other studies. However, no significant difference was found in the prevalence of thyroid diseases between the groups in our study. Besides, high levels of anti-TG and anti-TPO were observed in the RAS group. Significantly high levels of Anti-TG were seen. This can highly support the theory of autoimmunity in RAS pathogenesis and prompt us to order thyroid tests in such patients. Humans use many mechanisms to compensate iodine deficiency including overproduction of TSH that causes iodine assimilation and increases the conversion of T4 to T3. This is the same as our results (higher level of T3 and lower levels of T4 and TSH). Others have claimed that iodine mouthwash shows significant therapeutic effects for RAS. RAS can be a symptom of iodine deficiency; which should be further studied [16].

Our results were different from other studies which reported insignificant results; this may be explained by the mean age, the period of time that our patients were suffering from RAS, the oral ulcers in each period and blood sample taken in 1-3 days of each period. We matched both groups for hemoglobin, hematocrit, folic acid, vitamin B12 and Fe to eliminate their confounding effects.

Group	Age	Mean age	±SD	Females	Males
Case	18-42	28.5	5.8	28	22
Control	19-45	27.3	5.4	33	17

Table 1. Distribution of age and sex.

Normal range		Min	Max	Patient group (Mean ± SD)	Control group (Mean ± SD)	P-value
FT3pg/mL	1.9-4.3	1.61	5.57	3.045 ± 1.20	0.71 ± 2.782	0.031
FT4ng/dL	0.7-1.8	1.22	3.61	0.465 ± 1.623	0.419 ± 1.889	0.447
TSH	0.32-5.2	0.17	3.01	1.24 ± 1.398	1.14 ± 1.178	0.706
mlu/L						
Anti-TG	<4	0.49	57.5	21.90 ± 7.772	8.28 ± 2.919	0.008
Au/Ml	Normal					
	>4Elevate					
	d					
Anti-TPO	<40	0.0	499.1	57.695 ±	34.489 ±	0.067
Iu/mL	Negative			129.73	105.26	
	>40					
	Positive					

Table 2. The values of hormones and autoantibodies, SD and P -Values.

Anti–TPO		Anti–TG	Anti-TPO and Anti-TG	Total
Case n=50	(18%)9	(24%)12	(12%)6	(54%)27
Control n=50	(12%)6	(8%)4	(2%)1	(22%)11

Table 3. Prevalence of thyroid autoantibodies in the study group.

Euthyroid (n)		Hypothyroid (n)	Subclinical hyperthyroid (n)	Hyperthyroid (n)	FT3 (Mean ± SD)	FT4 (Mean ± SD)	TSH (Mean ± SD)
Case n=50	45(90%)	1(2%)	3(6%)	1(2%)	3.045 ± 1.20	1.623 ± 0.465	1.398 ± 1.24
Control n=50	45(90%)	0	4(8%)	1(2%)	2.782 ± 0.71	1.889 ± 0.419	1.178 ± 1.14

Table 4. Status of autoimmune thyroid disorders and thyroid hormone levels in the control and patient groups.

Conclusion

This study showed that thyroid antibodies should be tested in RAS patients in order to rule out thyroid diseases. We propose more studies in this field with larger sample sizes.

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Conflict of interest

There is no conflict of interest to declare.

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