Ocular surface and salivary gland involvement in patients with autoimmune thyroid disease

Superfície ocular e envolvimento da glândula salivar em pacientes com tireoidite autoimune

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ABSTRACT

Purpose: *Many reports have indicated an association between thyroid dieases and primary Sjögren's syndrome (pSS). The aim of our study was to evaluate the outcomes of the tests used for dry eye diagnosis and salivary gland involvement in patients with autoimmune thyroiditis.* ***Methods:*** *Forty-two patients (group 1) with autoimmune thyroid disease and 30 controls (group 2) were selected. Tear film break up time, Schirmer I test, Schirmer II test, ocular staining with 1% rose Bengal and salivary gland cintilography were performed in both groups.* ***Results:*** *Regarding the ocular surface damage observed by Rose Bengal test there was no difference between groups (p=0.77). For tear film break up time the groups did not differ statistically (p=0.46). There was no statistical difference between groups 1 and control in scintigraphy of the salivary gland (p=0.99). A statistical difference between the patients with thyroid disease and the control group was seem only in the Schirmer II test (p=0.0009).* ***Conclusion:*** *No patients fulfilled all criteria for Sjögren's syndrome. It is possible that it could be underestimated.*

Keywords: *Autoimmune thyroid disease; Sjögren's syndrome; Lacrimal gland; Hashimoto's disease; Dry eye syndrome*

RESUMO

Objetivo: Muitos trabalhos mostraram uma associação entre doenças da tireoide e síndrome de Sjögren primária (pSS) . O objetivo do nosso estudo foi avaliar os resultados dos testes utilizados para o diagnóstico de olho seco e envolvimento das glândulas salivares em pacientes com tireoidite autoimune. **Métodos:** Quarenta e dois pacientes (grupo 1) com doença autoimune da tireoide e 30 controles (grupo 2) foram selecionados. Nos dois grupos foi realizada a mesma sequência de exames: tempo de ruptura do filme lacrimal, teste de Schimer I, teste de Schirmer II, avaliação da córnea e conjuntiva com corante de Rosa Bengala. Também foi realizado cintilografia da glândula salivar para avaliar seu envolvimento. **Resultados**: Em relação aos danos na superfície ocular observado pelo teste rosa bengala não houve diferença entre os grupos (p=0,77), o mesmo ocorrendo no tempo de ruptura do filme lacrimal (p=0,46) e na cintilografia da glândula salivar (p=0,99). Apenas no teste de Schirmer II houve diferença estatística significante (p=0,0009). **Conclusão:** Nenhum paciente cumpriu todos os critérios para a síndrome de Sjögren. É possível que este resultado esteja subestimado.

Descritores : Doença autoimune da tireoide; Síndrome de Sjögren; Glândula lacrimal; Doença de Hashimoto; Síndrome do olho seco

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Introduction

Sjogren's syndrome (SS) is a cronic systemic autoimmune inflammatory disease, whose targets are exocrine glands, mainly lacrimal and salivary. It is also known as Sicca syndrome due to diminished secretion by these glands, that are infiltrated by an intense lymphoplasmocytic reaction[1]. SS can be a primary exocrine gland disease (pSS) or be associated with other autoimmune diseases as secondary SS[2]. Depending on its diagnostic criteria and the population studied, SS was estimated to affect between 0,05% and 4,8% of adults[3].

Although the disease affects primarily the salivary and lacrimal glands in it's early stage, it can subsequently involve other organs or systems of the body such as the lungs, kidneys, thyroid, the circulatory system and central nervous system[4]. Thyroid autoimmune diseases have been described in many cases of primary SS. Among these, two entities can be highlighted: Graves disease and Hashimoto's thyroiditis, both are characterized by an intense immune response to thyroid selfantigens: thyroglobulin, thyroperoxidase and thyrotropin receptors[5]. There are some similarities between the imunopatology of thyroid autoimmune diseases and SS sialoadenites: activated T linfocyte infiltrates, B cells clonal expansion and the inappropriate expression of class II human leucocyte antigens (HLA). Beyond this, both share a genetic connection by HLA- DR3/DR4 alleles. Dias et al. demonstrated the presence of thyroid hormone receptor in lacrimal gland, cornea and conjuntiva epithelial cells. This finding associated with augmented expression of this receptor in patients with hypothyroidism indicates that lacrimal gland is a target organ for thyroid hormone[6].

There are still controversies about the association of these two diseases due to different results in literature. Pioneer studies found an association between both conditions in 10%[7], 14%[8], and 18%[9] of cases. In a study performed by Karsh and Perez E et al., 50% of primary SS presented antithyroid antibodies and signs of thyroid disfunction reflected by increased TSH level[10]. Anderson et al. showed an increased prevalence of antithyroglobulin antibodies in SS patients, but SS prevalence in patients with autoimmune thyroiditis is still poorly researched[11].

To our knowledge, few studies have investigated the association between pSS and thyroid disorders prior to their pSS diagnosis. The aim of our study was to explore the risk of pSS in patients with thyroid disease.

Methods

This cross sectional study was performed at the corneal and external disease department of Hospital do Servidor Público Estadual de São Paulo (SP), Brazil. The research protocol was approved by Ethics and Research Committee, with number 0115/09.

The study group

Inclusion criteria: patients with clinical and serologic diagnosis of Hashimoto's or Graves' thyroiditis, with anti-peroxidase level > 100UI/mL (value of reference 0-35) and anti-TSH receptor antibody level > 1.75UI/mL (value of reference until 1.75UI/mL). All patients were of age and signed the term of consent.

Exclusion criteria: patients using ocular medication or contact lens within 7 days prior to evaluation, patients with previously diagnosed ocular diseases which compromise lacrimal production or drainage (Sjögren's syndrome, Stevens Johnson syndrome, ocular pemphigoid, chemical burn, trachoma, meibomian disfunction), continuous use of anticolinergic medications, pregnants and lactants, Graves disease with NO SPECS[12] classification > 1 (only signs, no symptons/ lid retraction,stare, lid lag), table 1.

The control group

Inclusion criteria: patients without clinical and serologic diagnosis of Hashimoto's or Graves' thyroiditis who sought outpatient service for a routine. All patients were of age and signed the term of consent.

Exclusion criteria: patients using ocular medication or contact lens within 7 days prior to evaluation, patients with previously diagnosed ocular diseases which compromise lacrimal production or drainage (Sjögren syndrome, Stevens Johnson syndrome, ocular pemphigoid, chemical burn, trachoma, meibomius disfunction), continuous use of anticolinergic medications, pregnants and lactants.

Clinical examination

The most accepted criteria for SS diagnosis are the ones presented at American-European consensus[13], which are: a) minor salivary gland biopsy showing focal sialoadenitis with lymphocytic infiltration with more than 1 focus/4mm^2 or a benign lymphoepithelial lesion localized in a major salivary gland; b) Rose Bengal staining demonstrating corneo-conjunctival compromise, and reduction of tear meniscus or reduction of tear

Table 1

Classification of Graves' eye disease (mnemonic no specs)

Class 0 - no signs or symptoms
Class 1 - only signs (limited to upper eyelid retraction and stare, with ou without lid lag)
Class 2 - soft tissue involvement (conjuntival and eyelid edema, conjuntival injection, etc.)
Class 3 - proptosis
Class 4 - extraocular muscle involvement
Class 5 - corneal involvement
Class 6 - sight loss (due to optic nerve involvement)

film break up time or Schirmer's test (without anesthetic) less than or equal to 5mm in 5 minutes[14]. We chose not to perform a biopsy of the salivary gland due to its invasive nature, but to assess the salivary impairment objectively we used the salivary gland scintigraphy. Keratoconjunctivitis sicca was diagnosed when: rose bengal staining was greater than 4 on a scale of van Bjesterveld[15], Schirmer I and II below or equal to 5 mm and tear film break up timeless than 10 seconds. SS was defined by the presence of keratoconjunctivitis sicca and xerostomia.

There is no consensus in the literature regarding the ideal sequence for tests of dry eye, so that the proposal in this study was designed to avoid the most that conducting a test influenced the performance of the next test. The scintigraphy of the salivary gland was subsequently performed ophthalmologic evaluation. All patients in both groups were evaluated by the same researcher (who didn't know wich group the patients were) according to the following sequence:

- Tear film break up time: The examination was performed with a slit lamp and illumination of cobalt. A drop of 1% fluorescein was instilled into the lower fornix of both eyes of the patients. Patients were asked to blink a few times and then stop blinking when the timer was immediately fired. The length of time of appearance of the first break point of the tear film on the corneal surface. Three measurements were recorded so that the average was obtained.

- Schirmer I test: Also called the Schirmer's test without topical anesthesia was performed simultaneously in both eyes, placing the lateral third of each of the lower eyelids and standardized millimeter strip of filter paper Wathman number 41 (Ophthalmos, São Paulo, Brazil). Patients were instructed to remain with eyes closed for five minutes.

- Schirmer II test: same procedure as above plus nasal stimulus with a swab.

- Rose bengal: realized thirty minutes after the Schirmer test. Was applied to the superior bulbar conjunctiva of each eye a micro drop of rose bengal 1% (Ophthalmos) using a capillary tube of plastic. Then, patients were evaluated at the slit lamp with lighting and light filter anerita. Each eye received a score of 0-9, based on the sum of the degree of staining of the conjunctiva lateral, medial conjunctiva and cornea, according to the classification proposed by Van Bijsterveld, 0 being absence of commitment and 9 maximum damage.

- Salivary gland scintigraphy: held in gamma camera, the above incidences, and extended side after intravenous introduction of 99m Tc-free.

Statistical Analysis

The paired Student t test was used to assess the existence of difference between Schirmer 1 and 2 in the case group. The paired Student t test was used to assess the existence of difference between Schirmer 1 and 2 in group control. The Student t test was used to assess the existence of differences between the Schirmer 1 in the case group and Schirmer 1 in the control group. The Student t test was used to assess the existence of difference between Schirmer 2 in the case group and in the control group. The Mann-Whitney test was used to assess the existence of difference between Rose Bengal in the case group and Rose Bengal in the control group. The Fisher exact test was used to assess the existence of differences between radionuclide scintigraphy in the case group and the control group. The Fisher exact test was used to assess the existence of difference but in the case group and the control group. The significance level was 5%. The tests were performed using the software GraphPad Prism 5.00 (GraphPad Software, San Diego, USA)

Table 2

Average and standard deviation from Schirmer's test

	Case group	Control group	p[1]value
Schirmer 1	12.67mm ± 9.03	12.70mm ± 10.33	0.99.
Schirmer 2	14.14mm ± 7.37	20.53mm ± 8.14	0.0009

[1] p value from t student test; case group versus control group
[2] p value from paired t student test. Schirmer 1 *versus* Schirmer 2

Table 3

Median, maximum value and minimum value from Rose Bengal test

	Case group	Controlgroup	p[1]value
Median	0	0	0.77
Minimum-maximum	0 - 9	0 - 4	

[1] p value from t Mann-Whitney test; case group *versus* control group

Table 4

Tear film break up time results

	Case group	Control group	p[1]value
<10s	17	9	0.46
>10s	25	21	

[1] p value from exact Fisher test

Table 5

Scintigraphy results

	Case group	Control group	p[1]value
normal	7	6	0.99
salivary gland involvement	14	10	

[1] p value from exact Fisher test

Results

Were selected according to the criteria mentioned, 42 patients with autoimmune thyroid disease (group 1), 30 with hypothyroidism , 12 patients with Graves' disease and 30 without control group (group 2). In group 1, 31 patients were female and 11 were male and mean age 42.85 years (range 26-73 years). In the control group, 26 patients were female and 4 male and mean age was 55.8 years (range 31-85 years) .

In group 1, 37 patients (88.1%) were treated for thyroid dysfunction with levothyroxine monotherapy and 5 patients (11.9%) were taking propylthiouracil.

Just 21 patients from group 1 underwent salivary gland scintigraphy and 16 patients from control group.

Table 2 show a statistical difference between groups 1 and 2 only on the Schirmer II test (p=0.009).

With respect to ocular surface damage observed by Rose Bengal test there was no difference between groups (p=0,46), table 3 .

For the time of the tear film break the groups did not differ statistically (p=0.99), table 4 .

According to table 5, there was no statistical difference between groups 1 and 2 in scintigraphy of the salivary gland (p=0.99).

Discussion

Prevalence studies have shown different results. The large variability could be explained by differences in genetic and environmental factors, but primarily it may also reflect on differences in the methodology. Many classification criteria for SS had been proposed, modified, and revised before and during the International Symposium in Compenhagen in 1986. Nowadays, in spite of some limitations, the American- European Consensus is used widely to classify SS[16].

Studies had pointed that more than 45% of patients with primary SS develop most commonly autoimmune thyroid disease[17]. D'Arbonneau and cols.[18]confirmed that thyroid disease is 30% more common in patients with primary SS compared to control group .

But few have published works on the prevalence of primary SS in patients with autoimmune thyroiditis as we did in this study. Ramos-Casals et al. found no significant difference in the prevalence of thyroid disease compared with patients of the same sex and age (with or without primary SS)[19]. Williamson et al. found no increased prevalence of primary SS patients with thyroid diseases to carry out evaluation of the tear film (Schirmer test, rose bengal) and also showed that control patients had abnormal sialography examinations more frequently than the disease group[20]. Finally, Petri et al., reported that there was no increase in the frequency of rheumatic symptoms, including dry eyes and mouth, and systemic autoantibodies except anti-nuclear factor (ANF) but including anti-Ro and anti-La, in patients with autoimmune thyroiditis compared to patients with not autoimmune thyroid disease[21].

In the study by Hansen et al. 19/63 patients enrolled were tested for xerostomia by sialometry and/or salivary gland biopsy and keratoconjunctivitis sicca by three objective tests. Six of these had keratoconjunctivitis sicca and xerostomia, while 2 of these 6 had autoimmune sialadenitis in the biopsy of lip[9]. Coll et al. studied the prevalence of xerostomia and keratoconjunctivitis sicca in 176 asymptomatic patients with autoimmune thyroiditis. Nineteen of the 52 patients tested for xerostomia by salivary gland scintigraphy and/or gland biopsy and 9/170 patients examined for keratoconjunctivitis sicca by Schirmer's test and Rose Bengal had positive results. The authors reported that SS was diagnosed in 24% of patients. SS was defined by the presence of keratoconjunctivitis sicca and/or xerostomia[22].

Another factor that must be considered in our study is the influence of age for both eye tests and the oral test[14]. Both Schirmer test and tear film breakup time show inversely data proportional to age. In addition, postmenopausal women occur with decreased levels of androgens , a situation which leads to an imbalance of the ocular surface and tear film [23]. This may explain the absence of statistical difference between the two groups regarding the Schirmer test and the tear film break up time. The Schirmer II test (with nasal stimulation) was the only one to show a statistical difference compared to the control group, confirming that this test is the most accurate to demonstrate change in tear function and should be used as screening in patients with likely SS[24]. The Rose Bengal test was inconclusive in our study, against the results of Coll[22], which showed positivity in 23 % of 170 patients.

The fact that only 21/42 patients from group 1 and 16/30 patients in group 2 had the examination of salivary gland scintigraphy was due to the fact that it is an uncomfortable method. Wernicke et al. reported that ultrasonography has a specificity greater than 90% and sensitivity close to 60% to demonstrate changes of submandibular glands in patients with SS and it's a noninvasive and therefore good option for SS diagnosis[25].

It is known that after the commencement oflevothyroxine sodiumhormone replacement, serum TSH takes about 4 to 8 weeks to settle. In group 1, all patients were being treated but it was not taken into account: disease duration and treatment time. It is presumed that replacement with levothyroxine may have eliminated symptoms in patients studied here, however no study has clearly shown the action of this drug in the tear film.

It would be interesting to include in the research dosage of anti-Ro/anti-La since they are positive in approximately 60% of SS patients, even not being organ-specific autoantibodies[26]. It is also known that the identification of anti-Ro/La at the beginning of SS demonstrates that these patients have a greater chance of developing thyroid dysfunction[18]. Tektonidou et al. published that SS happens in 1/10 patients with thyroiditis autoimmune who have positive antinuclear antibodies (ANA)[27], being suggested by others to search in all patients with severe dry eye[28].

The data presented in this study, showed that assessments of tear function tests and salivary gland involvement in patients with autoimmune thyroid diseases had no significant differences compared with the control group. Some factors limit the interpretation of the data, the small sample of patients, the heterogeneity of the disease diagnosis time and the fact that the evaluation was done in a short period of time. No patients fulfilled all criteria for Sjögren's syndrome.

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