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Research Article

Changes of Tear Function Tests in Patients with Hashimoto Disease

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Abstract

Purpose: Measurement of tear function tests in patients with Hashimoto disease (HD), and comparing the results with the control group.

Methods: One hundred seventy three patients with Hashimoto disease (57 hypothyroid, 81 euthyroid, 35 hyperthyroid) who was under the follow up of Department of Endocrinology, and 56 sex-age matched healthy individuals as the control group were included in the study. All participants underwent full ophthalmologic examination, Schirmer test and tear break up time (TBUT). The results were recorded for statistical analysis.

Results: Of the Hashimoto disease patients,159 were female and 14 were male. Schirmer's test results were recorded as 13.53 ± 8.10 mm in patients with Hashimoto disease, and 18.25 ± 6.32 mm in the control group. The difference between two groups was statistically significant ($p < 0.01$). However, no significant difference was found between the subgroups of Hashimoto disease according to the current thyroid function status. Tear break up time values were found as 15.39 ± 5.05 seconds in Hashimoto disease patients, and 15.67 ± 3.37 seconds in the control group ($p > 0.05$).

Conclusions: In patients with Hashimoto disease, Schirmer's test can demonstrate some deterioration before than the other tests. Complete eye examination is beneficial in early diagnosis and treatment of dry eye as well as other ocular complications in such patients.

Keywords: *Hashimoto Disease; Schirmer Test; Tear Break Up Time*

Introduction

Autoimmune attack in which antibodies directed against components of the thyroid gland leads to autoimmune thyroid disease (ATD). ATD, include both Graves' disease (GD) and Hashimoto's disease (HD) [1,2]. The prevalence of HD in the society from 0.9 to 2%, without any distinction of race, and it is almost 4 times more frequent in women than men [3-5]. ATD is the most common inflammatory illness of the thyroid and HD is the most common type of ATD [6,7].

Autoimmune thyroiditis is more common in subjects with tissue types HLA-B8 and HLA-DR5 [5,8,9] aphthous stomatitis, osteoarthritis, keratoconjunctivitis sicca, xerostomia and carpal tunnel syndrome) have been observed [6,10].

In the course of connective tissue diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjogren's syndrome (SS), antibodies develop against thyroid tissue and HD emerges as a consequence of inflammation. Chronic thyroiditis may either develop solely itself or may be associated with both organ-specific and systemic autoimmune diseases in patients with HD [8]. When HD is clinically in a subject, serum thyroxine (T4), thyroid stimulating hormone (TSH) and thyroid antibody measurements are sufficient for the diagnosis [4,5].

It is that there is a correlation between HD and SS [9,11,12]. Dry eye is a widespread clinical condition with inflammatory ocular surface disease affecting the quality of life significantly. The composition of tear has in lacrimal tear dysfunction; the equilibrium in ocular surface deteriorates and tissue damage are facilitated as a consequence of chronic inflammation. Tear dysfunction develops when the lacrimal functional unit (LFU) including the tear producing glands (lacrimal glands, conjunctival goblet cells, and meibomian glands) and their neural and immunological component, is unable to sustain a stable precorneal tear layer [4]. Dry eye syndrome and keratoconjunctivitis sicca are similar terms both are in a group of disease which is with specific ocular symptoms in conjunction with reduced or irregular tear production, or with increased evaporation from the ocular surface. It is a common chronic inflammatory disease in ocular surface, characterized by abnormity of tear film. The incidence was more prevalent in women and increased with age [13,14]. In this study, we investigated the tear function changes in patients with HD.

Materials and Methods

One hundred seventy three patients with HD who received levothyroxine treatment (57 hypothyroid), and non received levothyroxine (81 euthyroid and 35 hyperthyroid) who were followed up by Department of Endocrinology and 56 age-sex matched, healthy subjects as the control group were included in the study. In addition, the average dose of levothyroxine taken in patients with hypothyroid HD was 133.63 ± 61.38 µg/day. Local ethics committee gave approval for this research. The study protocol followed the guidelines of the Declaration of Helsinki.

The diagnosis guidelines (the sixth draft) provided by the Japan Thyroid Association) are shown in table 1 [15].

A. Clinical findings
B. Laboratory findings
1) Positive for anti-thyroid microsomal antibody or anti-thyroid peroxidase (TPO) antibody
2) Positive for anti-thyroglobulin antibody
3) Lymphocytic infiltration in the thyroid gland confirmed with cytological examination
C. A patient shall be said to have chronic thyroiditis if he/she has satisfied clinical criterion and any one laboratory criterion.
Notes
• A patient shall be suspected to have chronic thyroiditis, if he/she has primary hypothyroidism without any other cause to induce hypothyroidism.
• A patient shall be suspected to have chronic thyroiditis, if he/she has anti-thyroid microsomal antibody and/or anti-thyroglobulin antibody without thyroid dysfunction nor goiter formation.
• If a patient with thyroid neoplasm has anti-thyroid antibody by chance, he or she should be considered to have chronic thyroiditis.
• A patient is possible to have chronic thyroiditis if hypoechoic and/or inhomogeneous pattern was observed in thyroid ultrasonography

Table 1: *Guidelines for the diagnosis of chronic thyroiditis (Hashimoto's disease).*

Patients with clinically suspected HD were requested to have thyroid ultrasonography, thyroid function tests (TSH, free thyroid hormones-fT3 and fT4) and the levels of thyroid-autoantibodies (anti- thyroid peroxidase and anti-thyroglobulin antibodies) for accurate diagnosis. Venous blood samples were collected at 8 AM, and 9 AM after an overnight fasting period. The blood was at 4000 rpm for 10 minutes, and the sera were assayed for TSH, fT3 and fT4 by an automated chemiluminescent assay system (IMMULITE 2000, Diagnostic Products Corp., Los Angeles, Calif, USA). After the diagnosis had, obtained measurements were recorded for statistic analysis. Mean ages of the groups, age at diagnosis, status of thyroid function tests, disease duration and dose of levothyroxine they took were recorded. According to American-European Consensus Sjogren's Classification Criteria [15].

Sjogren syndrome for diagnosis, were performed tests include serum autoantibodies (Anti-SSA (Ro) or Anti-SSB (La)), Schirmer test and biopsy of salivary glands. Ocular and oral symptoms were found the evaluation of clinical and laboratory findings [16]. The participants underwent a complete ophthalmologic examination including visual acuity, pupillary reaction, ocular motility, external inspection, indirect ophthalmoscopy as well as Schirmer tests and tear break-up time (TBUT) as the tear function test. Symptoms those can be considered as subjective, such as eye burning-stinging- tearing-pain, and dry mouth were also questioned. The questions were McMonnies questionnaire [17]. In the Schirmer's test, open eyes are, standard strip paper is in the lower 1/3 lateral fornix (cul-de-sac), Fluorescein paper was located to lower fornix without anesthesia for the determination of TBUT. The patient was allowed to blink a few times. After whole corneal surface was stained, the elapsed time between the last blink till the formation of dry spots on the cornea (the black area where fluorescein staining disappeared) < 10 seconds was accepted pathological [18-21]. TBUT, was repeated 3 times, the mean was taken.

Statistics

Compliance of the numeric variables to the normal distribution was checked by the Kolmogorov- Smirnov test. In parameters with normal distribution, One way Anova test was used to compare the groups. Tukey HSD was used as a post hoc test. In descriptive statistics, Chi-square test was used to compare the percentages. Statistical analyzes were performed using SPSS for Windows version 11.5 software package, and $p \leq 0.05$ was considered statistically significant.

Results

The mean age of patients with HD was 42.6 ± 9.1, and the control group 40.4 ± 13.2, there was no statistically significant difference between these groups. In patients with HD, the mean age at diagnosis was 38.5 ± 13.2 years, and mean disease duration was found as 3.5 ± 5.2 years. According to the demographic characteristics of the patients were shown (Table 2).

	Number	Minimum	Maximum	Mean	Std. Deviation	Std. Error Mean
Age control group	57	16	85	40,37	13,188	1,747
Age Hashimoto	173	16	85	42,63	14,087	1,071
Diagnostic Age	173	0	35	4,65	5,510	
Duration	173	13	76	37,98	13,167	

Table 2

Between the control and HD groups, statistically significant difference was found in terms of eye stinging, burning and dryness ($p < 0.05$). There was no statistically significant difference between patients with HD and the control group in terms of eye pain and dry mouth. In our study, dry eye (11 eye dryness, 1 Sjogren) was recorded in 6.4% of the 173 HD patients. Female: male ratio was found approximately as 11.3 in patients with HD. The mean value of Schirmer's test results in patients with HD was 13.5 ± 8.1 mm, and in the control group it were 18.2 ± 6.3 mm. There were statistically significant differences between the groups ($p < 0.01$). TBUT values were 15. 4 ± 5.1 seconds in patients with HD, and 15.7 ± 3.4 seconds in the control group. No statistically significant difference was found between these groups.

The mean value of TSH measurements in patients with HD was 5.2 ± 14.3 mIU/L and in the control group, it was 1.7 ± 0.9 mIU/L. There was a statistically significant difference between the groups (p=0.006). The mean value of fT4 measurements in patients with HD was 1.3 ± 0.5 ng/dL, in the control group 1.1 ± 0.1 ng/dL. Statistically significant difference was found (p = 0.024) between these groups and this was an expected result. In patients with HD, 57 hypothyroidism, 81 euthyroidism and 35 hyperthyroidism were recorded. In the subgroups of HD patients which were hyperthyroidism, hypothyroidism and euthyroidism, TBUT average, Schirmer's test results, TSH and fT4 values were the main reason of dry eye in patients with autoimmune thyroid orbitopathy (ATO) is the inflammation of ocular surface and lacrimal gland [22,23]. Alfaris., *et al*. said that SS and ATD are often associated [24].

Nowak., *et al*. recorded that the earliest clinical manifestation of thyroid orbitopathy was the inflammation in periocular soft tissue [23]. Increased evaporation of the tear film layer due to lid retraction or exophthalmos is also very important in the pathogenesis of dry eye in ATO. Furthermore, the increase in the range of interpalpebral opening and exophthalmos induced by ATO was reported to cause more evaporation of the tears resulting in an increase in tear osmolarity and consequently leading to the development of dry eye [25]. ATD is an auto-immune disease being composed of both HD and Graves' disease [26]. In some cases, the consequences of tear dysfunction can be both functionally and occupationally cumbersome. Chronic eye irritation may adversely affect the quality of life [4].

In our study, among patients with HD, 57 subjects were hypothyroid (32.9%), 81 were euthyroid (46.8%), and 35 subjects were thyrotoxic (20.2%), there were no differences between patients and the control group in terms of dry mouth. Among TBUT, Schirmer's test, TSH levels and prevalence of dry eye no statistically significant difference was found. TSH values were within the expected limits according to the state thyroid functions. Bouanani., *et al*. studied 26 patients with SS, and they found hypothyroidism in 19% and thyroid disease in 31% of SS patients [26]. HD may present with goiter and either hyperthyroidism (uncommon), hypothyroidism (common), or euthyroidism (most common) [7]. Soy., *et al*. reported that were 77% of their patients with HD hypothyroid, 18% hyperthyroid, and 3.5% euthyroid [9].

In this study, although mean Schirmer's test values in patients with HD were statistically significant lower than the control group, but TBUT results were not statistically significant different. However, Nowak., *et al*. recorded that both TBUT and Schirmer's test results were found significantly lower than the control group in their patients with ATO [23]. Gürdal., *et al*. in their study of patients with thyroid orbitopathy, basal value of Schirmer test results were 8.92 ± 5.52 mm, the mean TBUT was 3.92 ± 2.18 sec, these values were significantly lower than our measures [27]. Altiparmak., *et al*. were found initially no significant difference in terms of TBUT and Schirmer between the patients with ATO and control groups but there was a significant difference in our study [28].

In previous studies, reported that HD is more common in women [29-32]. In our study, female/male ratio was found as 11.3. Hence, the disease dry eye disease obviously affects women more.

In this study, we detected statistically significant difference between the HD patients and control patients. In the control group, there was no patient with Sjogren disease while there was one patient with dry eye. Epidemiological studies conducted in different populations reported the rate of dry eye as 2 - 14.4% [4]. In the study of Tektonidou., *et al*. including 168 subjects, they reported that 7 patients had subjective xerophthalmia, 6 patients had subjective xerostomia. Additionally, 5 patients had keratoconjunctivitis sicca, 4 patients had xerostomia and 5 patients were diagnosed as Sjogren syndrome [29]. In a study evaluating patients with primary SS, in which the tear functions known to be affected, HD was reported to be seen 3 times higher than normal. In patients with SS, corneal damage was seen as stromal thinning, inflammation and function of sensory corneal subbasal nerves were inhibited due to metabolic changes and so secretion of tear fluid was decreased [33]. In a study, 30% of diagnosed cases of SS had chronic thyroiditis as a complication [3]. In previous studies, the most common complaints in patients with ATO were reported as eye burning, stinging and feeling of dryness. Their initial complaints were usually sensation of foreign body in the eye, redness of the lids and conjunctiva, edema, blurred vision, and retro-orbital pain [23,34,35]. In a case study, eye pain in the form of pressure was also mentioned as a complaint [36].

Significant difference between patients and the control group in terms of ocular involvement were found in our study. Tjiang., *et al*. recorded ocular involvement in 34% of patients with HD, and upper eyelid retraction more than 5 mm were observed in 1:4 of these patients [37]. Grzesiuk., *et al.* found that the rate of ocular involvement were 5 fold higher in women than men in autoimmune thyroid diseases [40]. In previous studies, there were reported that female to male ratio was 9.3:1 in patients with mild ophthalmopathy, 3.2:1 in those with moderate ophthalmopathy, and 1.4:1 with severe ophthalmopathy [28-31]. In our study, there was no statistically significant difference in the involvement of women and men in terms of eye burning, stinging and dryness; however, eye pain were statistically higher in men than women ($p < 0.005$). In patients with HD, orbitopathy may be present in every three states of thyroxin (fT4) (Hyper-Hypo-Eu) [25]. As a matter of fact in our study, there were no difference among the subgroups of HD patients in terms of ocular involvement.

In some cases, the consequences of tear dysfunction may make it difficult to practice the subject's occupation [7]. Buchholz., *et al*. found the impact of severe dry eye resulting in surgery on the quality of life similar to presenting to the hospital for dialysis or severe angina [38]. Tear break up time is a measure of the functional stability of the tear. If deteriorated, it indicates especially the defect in lipid and mucin. Schirmer's test, on the other hand, shows the amount of secretion in the aqueous component of tear [39-41]. In a study conducted, symptoms of dry eye were found to be increased inversely proportional to the amount of mucin on the ocular surface and to be associated with TBUT [42]. In our scarcity of production of aqueous humor determined by the Schirmer test may be a predictor of severe, symptomatic dry eye disease in the future.

Conclusion

In conclusion, in patients with HD, Schirmer's test of dry eye may be deteriorated before other tests. Examination of the eye in patients with HD for possible involvement may enable the early diagnosis and treatment of dry eye as well as other ocular complications. Hence, the clinical picture may be controlled before dry eye has got worse, and the involvement on the ocular surface can be avoided without damage. Thus, the patients with HD should be followed up in terms of early ocular involvement.

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