·Clinical Research·

Presence of thyroid –associated ophthalmopathy in Hashimoto´s thyroiditis

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Abstract

• AIM: To determine the prevalence of ophthalmopathy in Hashimoto´s patients and to make a comparison in subgroups of patients

• METHODS: The study involved 110 Hashimoto´s thyroiditis patients and 50 control subjects attending to the endocrinology department of the hospital. Subgroup classification of patients was made as euthyroid, subclinic and clinic in Hashimato´s thyroiditis. All patients were evaluated by a single experienced ophthalmologist for the prevalence and characteristics of eye signs.

• RESULTS: The overall prevalences of eye changes were 22.7% (25 patients) in patients and 4% (2 persons) in control subjects respectively (P=0.002). In patients the most common symptom was retrobulbar eye pain with or without any eye movement. Thirteen patients had significant upper eyelid retraction (11.8%). Six patients had eye muscle dysfunction as reduced eye movements in up gaze. In control patients one person had proptosis and another had lid retraction. The clinical activity score and classification of the ophthalmopathy did not show any significant differences among subgroups.

• CONCLUSION: The eye signs were mostly mild (22.7%) and the most common eye sign was the presence of upper eyelid retraction (11.8%). Additionally six patients had eye muscle dysfunction as reduced eye movements in up gaze. Therefore we recommend to make a routine ophthalmic examination in Hashimoto´s thyroiditis patients in order not to omit the associated ophthalmopathy.

• KEYWORDS: Graves' ophthalmopathy; Hashimoto's thyroiditis; upper eyelid retraction; thyroid-associated ophthalmopathy

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INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is an autoimmune disorder of the extraocular muscles and surrounding orbital connective tissue which is generally associated with Graves' disease (GD) [1,2]. Typical signs include upper eyelid retraction (UER), periorbital oedema, proptosis, and impairment of eye motility [3]. The pathophysiology of TAO remains unclear but sensitized T-cells and autoantibodies against thyroid-stimulating hormone receptor (TSH-r) located on thyroid cells, orbit muscles and fibroblasts are targeted in patients developing ophthalmopathy [4]. Although TAO generally occurs in patients with hyperthyroidism due to Graves' disease, it may accompany to Hashimoto's disease as well [5]. However, TSH-r hypothesis cannot explain TAO in Hashimoto's thyroiditis, because patients with Hashimoto's thyroiditis are usually negative for TSH-r [6]. Although a few cases have been reported, the spectrum of eye signs and their prevalences in Hashimoto's thyroiditis are not well documented [7-9]. The aim of the present study is to determine the prevalence of eye signs in patients with Hashimoto's thyroiditis.

SUBJECTS AND METHODS

The study involved 110 Hashimoto's thyroiditis patients and 50 control subjects attending to the endocrinology department of the hospital. The local ethics committee's approval was received for the study, and informed consent of the participating subjects was obtained. The diagnosis of Hashimoto's thyroiditis was based on standard clinical criteria and confirmed by thyroid function testing, thyroid antibody tests. Subgroup classification of patients was made as euthyroid, subclinic and clinic Hashimato's thyroiditis [10]. We also studied 50 age- and sex-matched healthy subjects with no personal or family history of any thyroid disease, goiter, ophthalmopathy or other autoimmun induced disorders among clinic staff. The laboratory findings of patients and controls, including plasma-free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels and tiers of thyroid

Table 1 The laboratory findings in patients and control subjects

Groups	*n*	fT4 (ng/dL)			TSH (μIU/mL)		
		Min	Max	Median	Min	Max	Median
Patients	110	0.06	2.30	1.17	0.2	99	3.5
Control	50	0.90	1.60	1.2	0.3	4.0	1.3

fT4: Free thyroxine (normal range:0.7-1.7 ng/dL); TSH: Thyroid stimulating hormone (normal range: 0.2-4.2 μIU/mL;).

Table 2 The laboratory findings in subgroup of Hashimoto's thyroiditis patients

Presence of HT	*n*	fT4 (ng/dL)			TSH (μIU/mL)			Anti TG (IU/mL)			AntiTPO (IU/mL)		
		Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median
Euthyroid	66	0.78	1.70	1.27	0.02	4.20	2.67	5	4000	145	5	1000	228
Subclinic	22	0.70	1.67	1.14	4.5	19.6	8.5	19	4000	281	10	625	280
Clinic	22	0.06	0.9	0.8	4.30	99	11.9	1	1416	245	3	729	316

fT4: Free thyroxine (normal range:0.7-1.7 ng/dL); TSH: Thyroid stimulating hormone (normal range: 0.2-4.2 μIU/mL); AntiTg: Antithyroglobulin (normal range 0-115 IU/mL); AntiTPO: Antithyroid peroxidase (normal range 0-35 IU/mL).

peroxidase (TPO) and thyroglobulin (Tg) antibodies of the subgroups are summarized in Table 1 and 2.

All patients were evaluated by a single experienced ophthalmologist for the presence of ophthalmopathy. The diagnosis of ophthalmopathy was based mainly on the clinical state (eyelid retraction, periorbital swelling, diplopia and others) [3]. The grade, severity, and activity of the cases were classified according to the NOSPECS classification and the clinical activity score (CAS)[11,12]. The lid retraction was assessed by measuring the upper eyelid margin-reflex distance, which is the distance between the centre of the pupillary light reflex and upper eye lid margin in primary gaze position. A measurement of 3-5 mm is considered as normal and greater than 5 mm was considered as UER [13]. According to Hertel measurements, difference of >2 mm between two eyes or proptosis of >17 mm was accepted as significant proptosis for the Turkish population studied[14].

Statistical analysis was performed using the Statistical Package for the Social Sciences version 13.0 (SPSS, Chicago, IL, USA). Datas were expressed as median levels. Paerson Chi square test was used for the comparison of categoric variables between two groups and Mann-Whitney U test was used for the comparison of continious variables between two groups. Finally, a P<0.05 was considered as statistically significant.

RESULTS

Characteristics of Hashimoto's thyroiditis patients and control groups are shown in Table 3. Sex and age prevalence was similar between two groups. We have examined 110 diagnosed patients and 50 healthy control subjects for eye and upper eyelid abnormalities. The overall prevalences of eye changes were 22.7% (25 patients) in patients and 4% (2 persons) in control subjects respectively. This difference reached statistical significance (P=0.002). In patients the most common symptom was retrobulbar eye pain with or without any eye movement. In control patients, one person had proptosis and another had lid retraction. According to the NOSPECS classification, one patient (0.9%) was class 1, 12 were (10.9%) class 2, 2 were (1.8%) class 3, 6 were (5.5%) class 4, whereas no patients were class 5 or 6 (Table 4). The disease was inactive (CAS score 0) in 85 patients; mildly active (CAS 1-3) in 23 patients; and active (CAS≥4) in 2 patients (Table 5). The CAS and NOSPECS did not show any significant differences among subgroups (Tables 6, 7). Thirteen patients had significant UER (11.8%). Six patients had eye muscle dysfunction as reduced eye movements in up gaze. All of these patients also had UER.

Table 3 Characteristics of patients and control groups

Parameters	Patients (n=110)	Control (n=50)	P
Age (mean±SD)	41±11	43±13	0.41
Sex (M/F)	7/103	3/47	0.93
Eye sign (%)	22.7	4	0.002
UER (%)	11.8	1	0.03
Exophthalmos	6.4	1	0.24

HT: Hashimoto's thyroiditis; UER: Upper eyelid retraction.

Table 4 NOSPECS classification of Hashimoto's thyroiditis patients

Class	Patients (n=110)	%
0	89	80.9
1	1	0.9
2	12	10.9
3	2	1.8
4	6	5.5

Table 5 Clinical activity score in Hashimoto's thyroiditis patients

CAS	Patients (n=110)	%
0	85	77.3
1	6	5.5
2	8	7.3
3	9	8.2
4	2	1.8

CAS: Clinical activity score.

Table 6 Clinical activity score among subgroup of Hashimoto's thyroiditis patients

Clinical stage of the disease	CAS (%)					P
	0	1	2	3	4	
Euthyroid	78.8	4.5	7.6	7.6	1.5	
Subclinic	72.7	9.1	13.6	4.5	0	0.63
Clinic	77.3	4.5	0	13.6	4.5	

CAS: Clinic activity score.

Table 7 NOSPECS classification in subgroup of Hashimoto's thyroiditis patients

Clinical stage of the disease	NOSPECS (%)					*P*
	0	1	2	3	4	
Euthyroid	81.8	1.5	9.1	3.0	4.5	
Subclinic	81.8	0	13.6	0	4.5	0.92
Clinic	77.3	0	13.6	0	9.1	

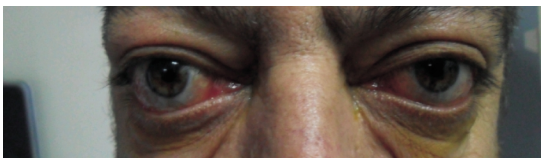

Figure 1 A patient with periorbital swelling, chemosis, conjunctival injection, and proptosis.

DISCUSSION

Thyroid-associated orbitopathy, is a set of symptoms, caused by an autoimmune process, typical for Graves' disease and rarely accompanies to Hashimoto's thyroiditis [15]. Immunologic crossreactivity of sensitized T lymphocytes and/or autoantibodies against thyroid and orbit may trigger the inflammatory process [16]. In both of Graves' and Hashimoto's disease, antithyroglobulin and anti-thyroid peroxidase antibodies are detected. Therefore a transformation of Graves' disease into Hashimoto's thyroiditis disease and the reverse is also known [6]. Typical signs are upper lid retraction, proptosis, periorbital oedema and restrictive myopathy[3]. Although numerous studies have been reported about the prevalence of Graves' ophthalmopathy, similar studies about the prevalence of Hashimato's ophthalmopathy are sparse. The first study about the prevalence of ophthalmopathy in Hashimoto's thyroiditis was reported by Tjiang *et al* [13], he studied 91 recently diagnosed patients with Hashimoto's thyroiditis and reported that the overall prevalence of any eye signs was 34% and about one third of patients had UER. Besides, two patients had eye muscle dysfunction and about a third of the patients had severe inflammatory changes such as periorbital swelling, chemosis, conjunctival injection, and proptosis (Figure 1). In the present study we studied the prevalence of ophthalmopathy in 110 Hashimoto's thyroiditis for eye signs and compared these with healthy control subjects. We showed that the prevalence of eye signs were 22.7% in patients, which were less than Tjiang's study, and 4% in control subjects and the difference reached a statistical significance (P=0.002). In patients, 11.8% had UER, 6.4% had proptosis, 5.5% had ocular myopathy as shown on Table 3. We also determined the possible effect of the clinic stage on ophthalmopathy, neverthless the CAS and NOSPECS classification did not show any significant difference among these subgroups. One of the important characteristics of our study which differs it from Tjiang's study is that we studied with larger number of patients and compared with healthy subjects that could enhance the power of the study. The levator palpebrae superioris and extraocular muscle involvement in Hashimoto's thyroiditis is common and has been emphasized in some studies. Grzesiuk *et al* [8] reported a 36-year-old man with Hashimoto's thyroiditis who had enlargement of the medial and inferior rectus muscles bilaterally, with eye pain, conjunctival redness, swelling of the eye lid and exophthalmos. Hiraga *et al* [7] reported a 76 years old woman with Hashimoto's thyroiditis suffering from diplopia due to limitations of upper gaze in the right eye. She had enlargement of inferior rectus muscle unilaterally. In an another study reporting two cases with Hashimoto's thyroiditis, the CAS activity score was found high and magnetic resonance imaging (MRI) showed enlargement of the extraocular muscles in both patients who required systemic glucocorticoid therapy and orbital irradiation to treat the TAO[9]. In our study 6 (5.5%) patients had ocular myopathy whom also had UER. Since patients with Hashimoto's thyroiditis are negative for TSH-r, the TSH-r hypothesis can not be used to explain the eye muscle involvement in Hashimoto's thyroiditis.

Specific antibodies against eye muscle antigens such as calsequestrin, collagen XIII flavoprotein (Fp) and G2s ,which are also shown to be goodmarkers of eye muscle damage in Graves patients may be an alternative explanation for eye muscle damage in Hashimoto's thyroiditis [17-20]. A study showed that calsequestrin and collagen XIII antibodies are also associated with chronic upper eyelid retraction as a dominant feature of ophthalmopathy in patients with Graves' disease and Hashimoto's thyroiditis [20]. Gopinath *et al* [21] evaluated 11 Hashimoto's thyroiditis patients for the presence of antibodies aganist eye muscle antigens and found that 7 patients were positive for at least one antibody. Five of them were found to have developed ophthalmopathy at first visit or on follow-up. In his study, calsequestrin and Fp antibodies were found to be the most frequently detected antibodies. Gopinath *et al* [22] presented an euthyroid woman with chronic UER and positive calsequestrin and collagen XIII antibodies who developed Hashimoto's thyroiditis and hypothyroidism 22mo later. Since the important of the eye muscle antibodies, particularly calsequestrin were stated in the majority of the studies, we think that they may be used as indicator tests to predict the muscle involvement to indicate the onset of eye muscle inflammation, with the possibility of early treatment. But unfortunately we were not able to study the serum levels of muscle antibodies in our study.

To summarize the main findings, the eye signs were mostly mild (22.7%) and the most common eye sign was the presence of UER (11.8%). Additionally six patients had eye muscle dysfunction as reduced eye movements in up gaze. On the other hand the clinical stage of the disease did not have any impact on the activity of ophthalmopathy. Even

though eyelid and extraocular muscle disorders may be a minor problem for most of the patients, they both may cause major cosmetic and functional complications requiring surgical management before the onset of the ophthalmopathy. Therefore we recommend to make a routine ophthalmic examination in Hashimoto's thyroiditis patients in order not to omit the associated ophthalmopathy.

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