

Demographic, clinical, laboratory, ultrasonographic, and cytological features of patients with Hashimoto's thyroiditis: results of a university hospital of 769 patients in Turkey

Mehmet Erdogan · Nihat Erdem · Sevki Cetinkalp ·
Ahmet Gokhan Ozgen · Fusun Saygılı ·
Candeger Yilmaz · Mehmet Tuzun · Taylan Kabalak

Received: 5 June 2009 / Accepted: 11 September 2009 / Published online: 24 October 2009
© Humana Press 2009

Abstract We investigated the demographic and clinical features of patients with Hashimoto's thyroiditis who had been diagnosed and treated in Ege University, the main referral center in the Aegean region of Turkey. Medical records of patients who had been followed in the endocrinology clinic of Ege University were retrospectively evaluated. Patients who had been diagnosed as having any thyroid disorder were determined. Patients with Hashimoto's thyroiditis were selected among those patients. Seven hundred and sixty-nine patients fulfilled diagnostic criteria for Hashimoto's thyroiditis (725 females, 44 males; mean age 41.76 ± 12.49 years). 62.7% of patients were between 30 and 50 years of age. 53.3% of females and 63.6% of males had diffuse enlargement of the thyroid gland. TSH level was above 4.0 IU/l in 25.6% of females and 27.4% of males. Anti-tyroglobulin antibody was positive in 92% of females and 93.2 % of males. Anti-thyroid peroxidase antibody was positive in 98.4 % of females (713 patients) and 100% of males. Thyroid ultrasonography demonstrated single nodule in 52.2% and multiple nodules in 11.3% of female patients; and single nodule 32% and multiple nodules in 20% of male patients. Fine-needle aspirations of the nodules were performed in 207 patients, and none of those biopsies was diagnosed as malignant. Women with suspicious biopsy were operated. After surgery, we found that, 2% ($n = 4$) of patients with FNAC diagnosis of suspicious

biopsies were papillary carcinoma and the other patients (3% ($n = 6$)) were lymphocytic thyroiditis. Age and sex distribution and laboratory findings of our patients were comparable to the previous reports. Nodule formation was the most common ultrasonographic finding in our patients, probably due to pseudonodularity. We found four women patients with thyroid cancer in our population.

Keywords Hashimoto's thyroiditis ·
Demographic and clinical features

Introduction

The first variety of chronic thyroiditis, struma lymphomatosa, was described by Hakaru Hashimoto in 1912 [1]. The term Hashimoto's disease or Hashimoto's thyroiditis is sometimes used to refer only to goitrous thyroiditis. However, it may usually be considered as a synonym of chronic thyroiditis or autoimmune thyroiditis, including atrophic and nongoitrous thyroiditis [1].

The diagnosis of autoimmune thyroiditis can easily be made by clinical findings and serological tests, especially in overt hypothyroidism. Presence of a diffuse goiter and positive antithyroid antibodies (antithyroglobulin antibodies and/or anti-TPO antibodies) without any evidence of other thyroid disease led to diagnosis of goitrous Hashimoto's thyroiditis. Thyroiditis is subclinical in about 90 % of patients. Hence, tests of thyroid function might be helpful. In patients who seem to have primary hypothyroidism with an atrophic thyroid, the existence of blocking-type anti-TSHR antibodies can be assessed, although their prevalence is low. The goiter of Hashimoto's thyroiditis may remain unchanged for decades, but usually it gradually increases in size [2–5].

M. Erdogan (✉) · S. Cetinkalp · A. G. Ozgen · F. Saygılı ·
C. Yilmaz · M. Tuzun · T. Kabalak
Department of Endocrinology and Metabolism, Ege University
Faculty of Medicine, 35100 Bornova, Izmir, Turkey
e-mail: drmerdogan61@yahoo.com

N. Erdem
Department of Internal Medicine, Ege University Faculty
of Medicine, Izmir, Turkey

The course may be clinically marked by symptoms of mild thyrotoxicosis, especially during the early phase of the disease. Symptoms and signs of mild hypothyroidism may be present in 20% of patients when first seen, or commonly develop over a period several years [6].

The clinical features and autoantibody profiles of Hashimoto's thyroiditis have been well documented. However, there are some unresolved issues such as association of Hashimoto's thyroiditis with thyroid cancer. Although Turkey is an endemic area for thyroid disorders, a detailed evaluation of clinical features of HT has not yet been performed in a large population of Turkish patients. Mild to severe degree of iodine deficiency was detected in the Aegean Region of Turkey [7].

In this study we outlined the demographic, clinical, laboratory, and sonographic features of our Hashimoto's patients, and compared our results with previous studies in the literature. We also documented the results of thyroid fine-needle aspiration biopsies. Several regions of Turkey, including the Aegean region, are well documented for increased prevalence of thyroid disorders. Our clinic is in Izmir and is the main referral center accepting patients from all over the Aegean region. Therefore, the patient population of Ege University can reflect the general population in that area.

Materials and methods

Medical records of patients who had been followed in the endocrinology clinic of Ege University were retrospectively evaluated. Patients who had been diagnosed as having any thyroid disorder were determined. Patients with Hashimoto's thyroiditis were selected among those patients. The inclusion criteria for the diagnosis of Hashimoto's thyroiditis were two out of the three of the following

1. Diffuse swelling of the thyroid gland without any other cause (such as Graves' disease)
2. Laboratory findings (positive anti-thyroid peroxidase (anti-TPO) antibody and /or positive anti-thyroglobulin antibody (anti-Tg) and /or Lymphocytic infiltration in the thyroid gland confirmed with cytological examination and /or evidence of a ultrasound hypoechoic pattern
3. Hypothyroidism

Age and sex distributions, frequencies of symptoms such as pain, palpitation and edema, physical examination findings, laboratory findings including thyroid function tests and autoantibodies, ultrasonographic and fine needle aspirations biopsy findings were evaluated in detail.

Descriptive statistics, chi-square test, Fisher's exact chi-square test, and Student's *t* test were used to for statistical analyses.

Results

Among 19750 patients who admitted to the endocrinology clinic of Ege University, 6496 patients (32.9%) were diagnosed as having various thyroid disorders, including thyroiditis, Graves' disease, toxic multinodular goiter, toxic adenoma, and single nodules. A total of 769 patients fulfilled the above-mentioned diagnostic criteria for Hashimoto's thyroiditis. The prevalence of Hashimoto's thyroiditis was 3.9% among the whole population of patients in our clinic ($n = 19750$), and its prevalence was 11.8% among patients with thyroid disorders ($n = 6496$).

Seven hundred and twenty-five patients were female ($n = 725$, 94%), and 44 patients were male ($n = 44$, 6%). Mean age of the whole group of patients with Hashimoto's thyroiditis was 41.76 ± 12.49 years. Age distribution was as follows: 16.4% of the patients were below 30 years of age, 62.7% of the patients were between 30–50 years of age, and 20.9 % of the patients were above 50 years of age.

Mean TSH level was 6.81 IU/l in the whole population of Hashimoto's thyroiditis patients. TSH level was above 4.0 IU/l in 25.6% of females, and 27.4% of males ($P > 0.05$).

Anti-thyroglobulin antibody was positive (N : 0–40 IU/ml) in 92% of female patients with Hashimoto's thyroiditis, and in 93.2% of males. Anti-thyroid peroxidase antibody was positive (N : 0–35 IU/ml) in 98.4 % of females and in 100 % of males (Fig. 1). There was no significant difference regarding the autoantibody profiles between female and male patients ($P > 0.05$).

Palpations of the thyroid glands of the female patients revealed that 19.5% of patients had normal thyroid examination findings, 53.3% had diffuse enlargement of the thyroid gland, 25.3% had single nodule, and 1.9% had multiple nodules. Examinations of male patients revealed

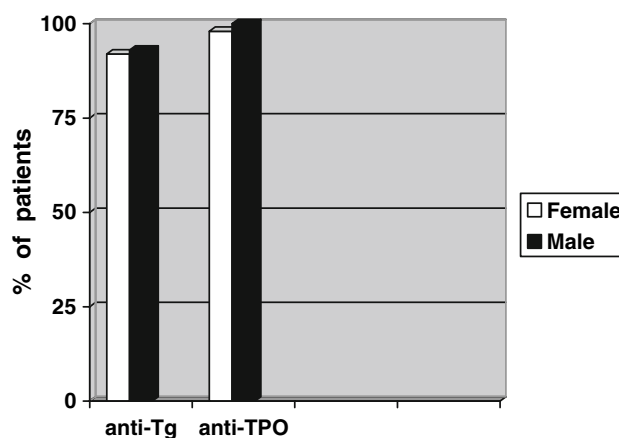


Fig. 1 Autoantibody profiles of patients with Hashimoto's thyroiditis (anti-Tg: anti-thyroglobulin antibody; anti-TPO: anti-thyroid peroxidase)

that 18.2% of patients had normal thyroid examination findings, 63.6% had diffuse enlargement of the thyroid gland, 15.9% had single nodule, and 2.3% had multiple nodules. Physical examination findings of males and females were comparable (Chi-square test, $P > 0.05$).

Thyroid ultrasonography demonstrated normal findings in 12.9%, diffuse enlargement in 23.6%, single nodule in 52.2%, and multiple nodules in 11.3% of female patients; and normal findings in 12%, diffuse enlargement in 36%, single nodule 32%, and multiple nodules in 20% of male patients (Table 1). There was no significant difference regarding thyroid ultrasonography findings between female and male patients ($P > 0.05$).

Fine-needle aspirations of the nodules were performed in 198 female and 9 male patients with Hashimoto's thyroiditis. None of those biopsies was diagnosed as malignant. Cytological results are as follows: Hashimoto's thyroiditis in 28%, benign nodular findings in 67%, and suspicious cytology in 5% of female patients; Hashimoto's thyroiditis in 33.3% and benign nodular findings in 66.7% of male patients (Table 2). Cytological examination findings were comparable between females and males (Chi-square test, $P > 0.05$). Women with suspicious biopsy were operated. After surgery, we found that, 2% ($n = 4$) of patients with FNAC diagnosis of suspicious biopsies were papillary carcinoma and the other patients (3% ($n = 6$)) were Lymphocytic thyroiditis. There was no significant difference regarding the malignant profiles between female and male patients ($P > 0.05$).

Table 1 Thyroid ultrasonography findings of patients with Hashimoto's thyroiditis

Thyroid USG findings	Female ($n = 725$) (%)	Male ($n = 44$) (%)
Normal	12.9	12.0
Diffuse enlargement	23.6	36
Single nodule	52.2	32
Multinodular goiter	11.3	20

Table 2 Cytopathological findings of fine needle aspiration biopsies (FNAB)

FNAB findings	Female ($n = 198$) (%)	Male ($n = 9$) (%)
Lymphocytic thyroiditis	28	33.3
Benign cytology	67	66.7
Suspicious cytology	5	0
Malign cytology	0	0

Discussion

In this study we presented the clinical, demographic, laboratory, and sonographic features of 769 patients with Hashimoto's thyroiditis who were diagnosed and treated in the endocrinology clinic of Ege University. Moreover, we documented the cytopathologic findings of 207 patients.

Similar to the results of previous reports, Hashimoto's thyroiditis was more prevalent in females between 30 and 50 years of age [4, 8]. The female/male ratio of our population was 16.4/1, and the mean age of our patients was 41.7. The most common physical examination finding was diffuse enlargement of the thyroid gland, which was also comparable to previous literature [4]. Diffuse enlargement of the thyroid was detected in 54% of females and 64% of males.

Thyroid function tests mildly elevated TSH levels in 25.6% of females and 27.4% of males at the time of diagnosis. Thyroid autoantibodies were present in more than 90% of the patients (anti-thyroglobulin antibody was positive in 92.8% of females and 93.2% of males; anti-thyroid peroxidase antibody was positive in 98.4 % of females, and 100 % of males). Thyroid function tests and autoantibody profiles of our patients was comparable to previous studies [4, 9, 10].

Ultrasonography is the most important imaging tool in the diagnosis of thyroid disease. The results of real-time B-imaging of the thyroid gland along with physical signs and basal TSH can aid in the diagnosis of thyroid dysfunction, of for instance, a small, hypoechogenic gland in Hashimoto's [11]. The positive predictive value for micronodulation in diagnosing Hashimoto thyroiditis is 94.7% [12].

Ultrasonographic findings in Hashimoto's thyroiditis are highly variable in different reports. Yarman et al. [11–13] demonstrated diffuse hyperplasia in 19 patients (39.6%), multinodular goiter in 20 patients (41.7%), and a solitary nodule in 9 patients among their population of 48 patients (18.7%) with Hashimoto's thyroiditis. In a series of 60 patients with autoimmune thyroiditis, 45 (75%) showed diffuse goiter, 6 (10%) showed multinodular goiter, and 9 (15%) had a solitary thyroid nodule sonographically [12–14]. In our study, we represented thyroid ultrasonography findings of 769 patients with Hashimoto's thyroiditis. We demonstrated normal findings in 12.9%, diffuse enlargement in 23.6%, single nodule in 52.2%, and multiple nodules in 11.3% of female patients; and normal findings in 12%, diffuse enlargement in 36%, single nodule 32%, and multiple nodules in 20 % of male patients. Hence, nodule formation (solitary or multiple) is the most common ultrasonographic finding in our patients, being present in approximately 60% of the patients. However, physical examinations of those patients revealed much lower rate of thyroid nodules. This discrepancy is most probably due to pseudonodule formation in Hashimoto's thyroiditis.

Papillary thyroid carcinoma (PTC) sometimes occurs with Hashimoto's thyroiditis (HT). It is often difficult to differentiate between benign and malignant nodules in Hashimoto's thyroiditis because Hashimoto's thyroiditis varies greatly on ultrasonography [15].

Some investigators have found an increased incidence of papillary carcinoma of the thyroid in patients with Hashimoto's (autoimmune) thyroiditis, which raises the possibility that there may be more than an incidental association between these two diseases [16].

The association between Hashimoto's thyroiditis and benign or malignant thyroid neoplasms has remained controversial. There are conflicting reports regarding cancer rate in patients with Hashimoto's thyroiditis. Carson et al. [17] found that only 4% of their patients had neoplasms. Ott et al. [18] found that among 267 patients with Hashimoto's thyroiditis 61 (23%) had coexistent carcinoma. Kurukahvecioglu et al. [19] showed that papillary thyroid carcinoma (18%) had coexistent Hashimoto's thyroiditis. Sclafani et al. [20] reported that 17% of 48 patients with Hashimoto's thyroiditis had concurrent cancer. Holmes et al. [21] demonstrated that cancer rate was 8.3% in their patients. Clark et al. [22] observed that 12% of patients with Hashimoto's thyroiditis developed thyroid cancer. In a population-based study of 829 patients, Holm et al. [23] could not find any increased risk for thyroid cancer except thyroid lymphoma. In our study, fine-needle aspirations of the nodules had been performed in 207 patients (198 females, 9 males), and none of those biopsies was diagnosed as malignant. After surgery, we found that, 2% ($n = 4$) of women patients with FNAC diagnosis of suspicious biopsies were papillary carcinoma. There was no significant difference regarding the malignant profiles between female and male patients. Papillary thyroid cancer (PTC), the most prevalent form of cancer in the thyroid, is 2.5 times more likely to develop in women than men. Given the relatively high prevalence of these diseases and the increased occurrence in women [24]. The low incidence thyroid cancer in our group may reflect population differences.

In summary we herein reported the demographic, clinical, laboratory, and sonographic features our patients with Hashimoto's thyroiditis. We demonstrated that age and sex distribution and laboratory findings of our patients were comparable to the previous reports. Nodule formation was the most common ultrasonographic finding in our patients, probably due to pseudonodularity. After surgery, we found four women patient with thyroid cancer in our population. To eliminate unnecessary surgical intervention, all patients should be evaluated by means of physical examination and thyroid autoantibodies, in addition to a thyroid scan, ultrasonography, and fine-needle aspiration biopsy when necessary. Our study was retrospective and presents the

usual limitations of a retrospective case–control design. On the other hand, since Ege University is the main referral center for endocrinologic diseases in the Aegean region of Turkey, our results can reflect the general population in that region.

References

1. H. Hashimoto, Zur Kenntniss der lymphomatosen Veränderung der Schilddrüse (struma lymphomatosa). *Arch. Klin. Chir.* **97**, 219 (1912)
2. A. Gordin, J. Maatela, A. Miettinen, T. Helenius, B.-A. Lamberg, Serum thyrotrophin and circulating thyroglobulin and thyroid microsomal antibodies in a Finnish population. *Acta Endocrinol.* **90**, 33 (1979)
3. S.M. Ling, S.A. Kaplan, J.J. Weitzman, G.B. Reed, G. Costin, B.H. Landing, Euthyroid goiters in children. Correlation of needle biopsy with other clinical and laboratory findings in chronic lymphocytic thyroiditis and simple goiter. *Pediatrics* **44**, 695 (1969)
4. W.M.G. Tunbridge, D.C. Evered, R. Hall et al., The spectrum of thyroid disease in a community. The Wickham Survey. *Clin. Endocrinol.* **7**(6), 481–493 (1977)
5. H. Tamaki, N. Amino, M. Kimura et al., Low prevalence of thyrotropin receptor antibody in primary hypothyroidism in Japan. *J. Clin. Endocrinol. Metab.* **71**(5), 1382–1386 (1990)
6. A. Gordin, P. Saarinen, A. Pelkonen, B.-A. Lamberg, Serum thyroglobulin and the response to thyrotropin releasing hormone in symptomless autoimmune thyroiditis and in borderline and overt hypothyroidism. *Acta Endocrinol.* **75**(2), 274–285 (1974)
7. S. Darcan, P. Unak, O. Yalman, F.Y. Lambrecht, F.Z. Biber, D. Göksen, M. Coker, Determination of iodine concentration in urine by isotope dilution analysis and thyroid volume of school children in the west coast of Turkey after mandatory salt iodization. *Clin. Endocrinol. (Oxf.)* **63**(5), 543–548 (2005)
8. P.A. Singer, Thyroiditis. Acute, subacute, and chronic. *Med. Clin. North Am.* **75**(1), 61–77 (1991)
9. S. Mariotti, S. Pisani, A. Russova et al., A new solid-phase immunoradiometric assay for anti-thyroglobulin autoantibody. *J. Endocrinol. Invest.* **5**(4), 227–233 (1982)
10. S. Mariotti, P. Caturegli, P. Piccolo et al., Antithyroid peroxidase autoantibodies in thyroid diseases. *J. Clin. Endocrinol. Metab.* **71**(3), 661–669 (1990)
11. B. Braun, W. Blank, Ultrasonography of the thyroid and parathyroid gland. *Internist (Berl.)* **47**(7), 729–746 (2006)
12. H.C. Yeh, W. Futterweit, P. Gilbert, Micronodulation: ultrasonographic sign of Hashimoto thyroiditis Micronodulation: ultrasonographic sign of Hashimoto thyroiditis. *J. Ultrasound Med.* **15**(12), 813–819 (1996)
13. S. Yarman, A. Mudun, F. Alagol, R. Tanakol, H. Azizlerli, H. Oguz, S. Cantez, Scintigraphic varieties in Hashimoto's thyroiditis and comparison with ultrasonography. *Nucl. Med. Commun.* **18**(10), 951–956 (1997)
14. S.M. Lai, T.C. Chang, C.C. Chang, S.H. Kuo, F.W. Chen, Sonographic presentation in autoimmune thyroiditis. *J. Formos. Med. Assoc.* **89**(12), 1057–1062 (1990)
15. N. Ohmori, M. Miyakawa, K. Ohmori, K. Takano, Ultrasonographic findings of papillary thyroid carcinoma with Hashimoto's thyroiditis. *Intern. Med.* **46**(9), 547–550 (2007)
16. M. Di Pasquale, J.L. Rothstein, J.P. Palazzo, Pathologic features of Hashimoto's-associated papillary thyroid carcinomas. *Hum. Pathol.* **32**(1), 24–30 (2001)

17. H.J. Carson, M.J. Castelli, P. Gattuso, Incidence of neoplasia in Hashimoto's thyroiditis: a fine-needle aspiration study. *Diagn. Cytopathol.* **14**(1), 38–42 (1996)
18. R.A. Ott, A.R. McCall, C. McHenry, H. Jarosz, A. Armin, A.M. Lawrence, E. Paloyan, The incidence of thyroid carcinoma in Hashimoto's thyroiditis. *Am. Surg.* **53**(8), 442–445 (1987)
19. O. Kurukahvecioglu, F. Taneri, O. Yüksel, A. Aydin, E. Tezel, E. Onuk, Total thyroidectomy for the treatment of Hashimoto's thyroiditis coexisting with papillary thyroid carcinoma. *Adv. Ther.* **24**(3), 510–516 (2007)
20. A.P. Sclafani, M. Valdes, H. Cho, Hashimoto's thyroiditis and carcinoma of the thyroid: optimal management. *Laryngoscope* **103**, 845–849 (1993)
21. H.B. Holmes Jr, A. Kreutner, P.H. O'Brien, Hashimoto's thyroiditis and its relationship to other thyroid diseases. *Surg. Gynecol. Obstet.* **144**, 887–890 (1977)
22. O.H. Clark, F.S. Greenspan, J.E. Dunphy, Hashimoto's thyroiditis and thyroid cancer: indications for operation. *Am. J. Surg.* **140**, 65–71 (1980)
23. L.E. Holm, H. Blomgren, T. Lowhagen, Cancer risks in patients with chronic lymphocytic thyroiditis. *N. Engl. J. Med.* **312**, 601–604 (1985)
24. D. Repplinger, A. Bargren, Y.W. Zhang, J.T. Adler, M. Haymart, H. Chen, Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer? *J. Surg. Res.* **150**(1), 49–52 (2008)