E-ISSN: 2616-3470
P-ISSN: 2616-3462

www.surgeryscience.com
2020; 4(2): 250-252
Received: 29-02-2020
Accepted: 31-03-2020

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A Study on thyroid profile among cases of Hashimotos thyroiditis

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DOI: https://doi.org/10.33545/surgery.2020.v4.i2d.451

Abstract
In autoimmune thyroiditis animal models, genetically determined immune defects have been suggestively linked to the breakdown of immunological self-tolerance that results in the presentation of host autoantigens and expansion of autoreactive lymphocyte clones. These immune and immune regulatory genes (i.e., CTLA-4 and others) are also involved. 100 consecutive patients with diagnosis of Hashimoto's thyroiditis were included in this study. Detailed clinical history and physical examination of the patients was done. Suspected patients were subjected to thyroid function test, FNAC, USG neck. The diagnosis was confirmed with serology. 69 percent of patients (65 females: 4 males) presented with hypothyroidism. 1 patient with associated orbitopathy had subclinical hyperthyroidism. 10 patients presented in euthyroid state. Most of them had associated goiters and many of them had associated pathologies of MNG or malignancy in them. 10 patients had subclinical hypothyroidism.

Keywords: Thyroid Profile, Hashimotos thyroiditis, MNG

Introduction
The development of the autoimmune failure of the thyroid is a multistep process, requiring several genetic and environmental abnormalities to converge before full blown disease develops. at the onset of disease, major histocompatibility complex (MHC) class II-positive antigen – Presenting cells (APC), particularly dendritccells, and different subclasses of macrophages, accumulate in the thyroid. APC present thyroid-specific autoantigens to the native T cells, leading to activation and clonal expansion of the latter. Thus, the initial stage of the disease is followed by a clonal expansion phase and maturation of autoreactive T and B lymphocytes in the draining lymph nodes [1, 2].

In an initial stage, antigen-presenting cells (APC), mostly dendritic cell and macrophage (Mq) derived, infiltrate the thyroid gland. The infiltration can be induced by an environmental triggering factor (dietary iodine, toxins, virus infection, etc.) which causes insult of thyrocytes and releasing of thyroid-specific proteins. These proteins serve as a source of self-antigenic peptides that are presented on the cell surface of APC after processing. Taking up relevant autoantigens, APC travel from the thyroid to the draining lymph node. A central phase occurs in the draining lymph node in which interaction between APC, autoreactive (AR) T cells (that survive as result of dysregulation or breakage of immune tolerance) and B cells result in inducing production of thyroid autoantibodies. In the next step, antigen-producing B lymphocytes, cytotoxic T cells and macrophages infiltrate and accumulate in the thyroid through expansion of lymphocyte clones and propagation of lymphoid tissue with in the thyroid gland. This process in preferentially mediated by T helper type 1 (TH1) cells which secrete regulatory cytokines (interleukn-12, interferon-y and tumor necrosis factor-a). In a final stage, the generated autoreactive T cells, B cells and antibodies cause massive depletion of thyrocytes via antibody-dependent, cytokine medicated and apoptotic mechanisms of cytotoxicity that leads to hypothyroidism and Hashimoto's disease [3].

In autoimmune thyroiditis animal models, genetically determined immune defects have been suggestively linked to the breakdown of immunological self-tolerance that results in the presentation of host autoantigens and expansion of autoreactive lymphocyte clones. These immune and immune regulatory genes (i.e., CTLA-4 and others) are also involved.

Breakdown of the immune tolerance might occur in severl ways including interrupting central tolerance (e.g. deletion of autoreative T cells in the thymus), defects in maintaining peripheral

Tolerance (e.g. activation-induced T-cell death and suppressing activity of regulatory T lymphocyte) and energy 9e.g. the expression of MHC class II molecules on non-professional APC). Animal models genetically predisposed to develop an autoimmune disease, and patients with AITD, showed a lack of, or a deficiency in, a subpopulation of regulatory T cells with suppressive function [4].

The mechanisms, whereby auto-reactive T cells escape deletion and energy, and become activated, remain uncertain. There is evidence that the thyroid cell itself, by "aberrantly" expressing MHC molecules, can play the role of "non-professional "APS and present disease-initiating antigen directly to the T cells. The concept of aberrant MHC class II expression was supported by studies in mice. They developed a type of Graves' disease (GD) after being injected with fibroblasts expressing MHC class II and the TSH receptor (TSHR). TPO antibody production was induced after injection with fibroblast co-expressing class II molecules and TPO.

Iodine is a necessary component of normal thyroid hormonogenesis. Incorporation of iodine into thyrosine residues of Tg leads to the formation of mono-iodotyrosine and di-idothyrosine derivates that subsequently undergo an oxidative coupling event resulting in the producing of T3 and T4. Iodine can promote antithyroid immunity in a number of ways. Several studies suggest that iodination of Tg is crucial for recognition by Tg-reactive T cells. Iodine excess can affect the Tg molecule directly. Creating new epitopes or exposing "cryptic" epitopes. It has been demonstrated that a higly iodinated thyroglobulin molecule is a better immunogenic than Tg of low iodine content. Therefore, highly iodinated Tg may facilitate antigen uptake and processing by APC. Additionally, high doses of iodine were shown to directly affect macrophages, dendritic cells, B and T lymphocytes, resulting in stimulation of macrophage myeloperoxidase activity, acceleration of the maturation of dendritic cells, increasing the number of circulating T cells and stimulating B cell immunoglobulin production. Excessive amounts of iodide ion are rapidly oxidized by TPO, thereby generating excessive amounts of reactive intermediates such as hypoiodous acid and oxygen radicals. These oxidative species damage thyrocyte cell membrane by oxidation of membrane lipids and proteins causing thyrocyte necrosis. The state of severe iodine deficiency itself namely leads to a lowering of thyroid autoimmunity and an immuno deficient state in autoimmune-prone BB-DP rats. This hampers the auto reactive T-cell generation and autoantibody production. A lower degree of Tg iodination also makes this molecule less antigenic [5, 6].

Methodology

100 consecutive patients with diagnosis of Hashimoto's thyroiditis were included in this study. Detailed clinical history and physical examination of the patients was done. Suspected patients were subjected to thyroid function test, FNAC, USG neck. The diagnosis was confirmed with serology.

After confirmation of diagnosis, patients were treated with levothyroxine at the standard dose of 1.6-1.8 mcg/kg lean body weight per day. A subset of patients was treated surgically.

The criterion for surgical intervention was

1. Presence of a nodule suspicious of malignancy\
2. Large goiter causing compressive symptoms
3. Painful hashimotos
4. Cosmetic

All candidates accepted for operative treatment underwent total thyroidectomy as per internationally accepted guidelines. The specimens of operated cases were routinely subjected to HPE examination to detect the associated pathologies, particularly malignancies. All patients in post-operative phase were put on levothyroxine.

Results

The most consistent serological marker in this study was anti TPO (positive in 90%). Anti tsh was the least consistent while anti tg was found to be elevated in 74% of the patients.

Table 1: Role of anti-thyroid antibodies

Antibody	No of Patients positive
Anti Tpo	90
ANTI Tg	74
Anti Tsh	09

FNAC is the single most useful investigation in diagnosis of thyroid disorders hashimotos notwithstanding a whopping 97 percent of patients could be assigned a diagnosis of hashimotos thyroiditis on the basis of FNAC features. FNAC picture in hashimotos is characterized by a hyper-cellular aspirate composed of a mixture of a mixture of lymphoid inflammatory elements and altered thyroid follicular cells. Compared to the degree of cellularity, colloid is absent.

USG on the other hand is a far less sensitive and specific investigation (51% sensitive). USG was particularly useful in diagnosis of coexisting pathologies for guiding FNAC. It was also useful for evaluating associated lymph nodes.

Table 2: Investigations

Investigation	No of Patients
USG Positive	51
USG Negative	39
USG Indeterminate	10
FNAC Positive	97
FNAC Negative	2
FNAC Indeterminate	1

Discussion

69 percent of patients (65 females: 4 males) presented with hypothyroidism. 1 patient with associated orbitopathy had subclinical hyperthyroidism. 10 patients presented in euthyroid state. Most of them had associated goiters and many of them had associated pathologies of MNG or malignancy in them. 10 patients had subclinical hypothyroidism.

Table 3: Percentage prevalence of anti-thyroid antibodies

Study	Present study	Erdogan *et al.* [7]	Jayaram *et al.* [8]
Anti TPO	90	98.4	90
Anti TG	74	76	83

Anti TPO was the most consistently elevated seromarker in all the series.

Therefore anti TPO may be considered the most reliable seromarker of this disease.

As the single most important investigation for diagnosis of the disease FNAC showed a high sensitivity of 97 percent. FNAC picture in hashimotos is characterized by hyper-cellular aspirate composed of a mixture of lymphoid inflammatory.

Elements and altered thyroid follicular cells. Compared to the degree of cellularit, colloid is absent.

Conclusion

Anti TPO antibodies and FNAC are the most diagnostic of investigations.

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