HASIMOTO’S THYROIDITIS A REVIEW

Ramya Ranganathan
Balasubramanian Thiagarajan
Stanley Medical College

Abstract:
Hashimoto thyroiditis is an organ specific autoimmune disorder. Initially described Hakaru Hashimotoa century ago is now the most common cause of hypothyroidism in iodine sufficient areas of the world. But still the pathogenesis is not fully understood. With higher incidence among female population HT develops as a result of interaction between the genetic factors and environmental factors in susceptible individuals. HT is associated with other autoimmune disorders. Now many variants of HT have been identified: classical form, fibrous variant, IgG4 variant, juvenile form, hashitoxicosis and silent thyroiditis (sporadic or postpartum).

All variants of HT are characterized by lymphocytic infiltration, destruction and atrophy of thyroid gland ultimately thyroid failure though each entity has specific other features. Clinically HT can also present as euthyroid or even hyperthyroid state with or without goiter. Diagnosis is based on the clinical features, demonstration of antibodies against thyroid antigen, sonography and cytological findings. Treatment is mainly supplementing Levothyroxin for correction of hypothyroidism. Surgery is reserved for patients with large goiter causing mechanical compression of cervical structures, painful HT and suspicion of malignancy.
Aim:
The aim of this article is to review the current knowledge of Hashimoto thyroiditis the most commonly encountered autoimmune thyroid disorder.

Search Strategy:
We searched in Google scholar, press.endocrine.org and various other scholarly sites using the terms “Hashimotos thyroiditis”, “chronic lymphocytic thyroiditis”, “autoimmune thyroiditis”, “thyroid autoantibodies” and collected all accessible relevant abstracts, research articles and review articles.

Introduction:
Hashimoto thyroiditis is the most common autoimmune thyroid disorder presenting commonly as diffuse goiter with hypothyroidism in areas of world where dietary iodine is adequate.

HISTORY:
Dr. Hakaru hashimoto discovered a new disease in 1912 based on histopathological study thyroidectomy specimens of four women with chronic thyroid disorders. He termed this disease as ‘struma lymphomatosa’ characterized by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy and eosinophilic changes in some thyroid follicles.

Until 1930s struma lymphomatosa was considered as early phase of riedel’s thyroiditis a stated by Simmonds et al and heineke et al but Allen Graham et al concluded that this disease was a separate entity and referred to as HASHIMOTO THYROIDITIS.

In 1950 Rose and Witebsky found thyroglobulin antibodies in rabbits injected with thyroid extracts which produced histological changes similar to HT. Deborah Doniah assessed the sera of patients with HT and found thyroglobulin antibodies. He also stated that HT is an autoimmune disease of thyroid gland.[1]

Incidence:
Hashimotos disease previously considered as an uncommon disease but now with the advent of newer technique it is possible to diagnose more number of cases. World wide Incidence is 0.3-1.5 cases per 1000 population per year. it is diagnosed 10-15 times more often in women than in men. Incidence increases with age and peaking at 45-65 years Prevalence is 4.5% (4.2% sub clinical and 0.3% clinical hypothyroid) based on biochemical analysis[6]. But with cytological diagnosis prevalence increases to 13.4%.the annual risk of the subclinical hypothyroidism to overt hypothyroidism is 4%. In the national health and nutrition examination survey III the prevalence of Tabs s 18% regardless of age and gender. The prevalence of Tabs is twice more common in women than in men and higher in whites and Asians than Blacks or Mexicans. HT appears to be more than 10% in patients with thyroid nodule. HT is associated with other autoimmune disorders like Addison’s disease, diabetes mellitus type 1, rheumatoid arthritis, systemic lupus erythematosus or vitiligo. The occurrence of papillary carcinoma thyroid in HT is extensively studied and the association ranges from 0.5-30% of cases.
Etiology:

The etiology of Hashimoto’s disease is multifactorial which arise from interaction between genetic and non genetic factors (environmental, dietary and existential).

The genetic polymorphisms of the Human leukocyte antigens (HLA) mainly HLA DR3 and DR5, T cell immune response genes like cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and protein tyrosine phosphate-22 (PTPN22), vitamin D receptor (VDR) and thyroid specific genes play a major role in pathogenesis. Single nucleotide polymorphism at thyroglobulin promotor site leads to activation of T cell response and polymorphism at CD40 gene leads to proliferation of B cells, antibody secretion and generation of memory cells. CTLA-4 and PTPN-22 are major negative regulators of cell mediated immunity. Depletion of regulatory T cell (Treg) leads to autoimmunity.[1][2]

Non genetic factors:

In genetically susceptible individuals the factors like excess iodine intake, infections, dietary deficiency of vitamins may initiate the autoimmune process.

These factors may act through epigenetic modifications like DNA methylation and histone modification at the tissue level which is evidenced by twin studies.

The association between iodine intake and HT has been extensively studied. More than adequate intake of iodine induces autoimmunity by various mechanisms like a) increasing the immunogenicity of thyroglobulin molecules exposing cryptic epitopes that facilitate presentation by APC and subsequent T cell activation, b) release of free radicals induce elevated expression of intracellular adhesion molecule-1 that attracts immunocompetant cells, c) free radicals damaging thyrocytes and exposing autoantigens, d) promoting follicular cell apoptosis by abnormal expression of TRAIL and its death receptor e) increased maturation of APC, B cells and T cells.
A country wide screening program done by AIIMS, Delhi has revealed that there is increased incidence of juvenile autoimmune thyroiditis including HT among the goitrous young girls in post iodinization phase in India. [5]

There are some evidence supporting the role of selenium and vitamin D deficiency in development of thyroid autoimmunity. Alcohol consumption and smoking seems to be protective against development of hypothyroidism in HT. drugs like INFalpha lithium, amiodarone, infections due to hepatitis C, Rubella, HSV EBV, Human T cell lymphotrophic viruses, exposure to chemicals like polyaromatic hydrocarbons, polyhalogenated biphenyls can trigger autoimmune thyroid disease.

The risk of Hashimotos thyroiditis and development of hypothyroidism increases with age. Female sex is associated with 8 fold increased risk for HT than male.

The possible mechanisms being effects of sex hormones, X-chromosome- encoded susceptibility, skewed X-chromosome inactivation, pregnancy and fetal microchimerism. Stress In any form and living In hygienic environment are risk factors for autoimmunity.

Pathogenesis:

Thyroid autoimmunity develops as a result of interaction of thyroid cells, APCs and T cells. The loss of immune tolerance leads to presentation of autoantigens and proliferation of autoreactive lymphocytes. MHC classII molecules expressed on the thyroid follicles of HT patients they are induced by viral infections or inflammatory cytokines.

They act as nonprofessional APCs and present self as well as foreign antigens initiating autoimmune response. The activated T helper cell stimulates B cell and plasma cells to produce antithyroid antibodies. INF gamma, TNF-alpha and IL-1 produced by Th1 cells activates macrophages that destroy thyroid follicles. Inflammation of the thyroid gland attract the immune cells. Regulatory T cells (Treg) play a major role in suppressing autoimmunization and cd8+ cell proliferation. But in AITD there is defective expression of genes for Treg cells. Another subset of t cells Th17 that are increased in HT. They act by inhibiting Treg cells and inducing local inflammation and fibrosis of gland.[26]

In HT there is increased expression of Fas ligand on the surface of thyroid follicular cells[13], increased proapoptotic protein and decreased Bcl2, thus inducing apoptosis. Animal models reveal that there is a role of TNF related Apoptosis Inducing Ligand (TRAIL) in protecting thyroid from fibrosis.[2][3][4][7][8][9].

Pathology:

In classic variant, the gland is usually diffusely enlarged. Firm in consistency and pale grayish On cut section.

Figure showing cut section of thyroid in Hashimoto
Microscopically the follicles appear small and the amount of colloid is reduced. There is extensive interstitial infiltration of mononuclear cells mainly B and T lymphocytes with some plasma cells and macrophages. Antibody producing plasma cells are polyclonal those containing IgG Ab are numerous. These lymphocytes are organized to form germinal centers. Some of the thyrocytes are enlarged, with hyperchromatic nucleus and eosinophilic cytoplasm due to abundant mitochondria called Hurthle cells or Oxyphillic cells which are characteristic of HT. In fibrous variant thyroid is large hard and lobulated because of fibrosis with in the capsule. In IgG 4 related variant there is pronounced lymphoplasmocytic infiltration with IgG4 producing plasma cells >20 cells per high power field.[11]

Fig 3: H&E showing Atrophic follicles with germinal center
Lymphocytic infiltration formation
And Hurthle cells

Fig 4: Showing
Clinical features:

Hashimoto’s thyroiditis presents at the age group of 40-60 years with female predominance. As painless enlargement of thyroid gland. Cases of painful goiter in HT have been reported. Clinically the patient can be euthyroid, hyperthyroid or hypothyroid based on the degree of thyroid destruction. Initially present with features of hyperthyroidism due to release of preformed thyroxine from the destroyed thyroid follicles. Then progress to subclinical and overt hypothyroidism ultimately thyroid failure. There can be local compressive effect of the goiter like dysphagia (esophagus), dysphonia (recurrent laryngeal nerve), dyspnea (trachea). In fibrous form thyroid appears lobulated with features of hypothyroidism. In fibrous atrophy variant gland may not be palpable presents as idiopathic myxedema. IgG4 variant present at 5th decade with female to male ratio of 3:1 has a rapid and aggressive course.

Juvenile variant present before the 18 years of age, usually asymptomatic. Hashitoxicosis variant has clinical features similar to graves hyperthyroidism initially but finally hypothyroidism evolves. Painless or silent variant occurs within 12 months after delivery. Also known as postpartum thyroiditis. Spontaneous recovery is possible after a period of time.[11]

Diagnosis:

Demonstration of antithyroid antibodies and ultrasonographic features confirms the diagnosis of HT.

*ANTI THYROID ANTIBODIES:

Antibodies against thyroid peroxidase and thyroglobulin are found in patients of HT. Antithyroid peroxidase antibody is considered as the best serological marker to establish the diagnosis of HT.

It is positive in about 95% of patients whereas anti thyroglobulin antibodies are positive in 60-80%.

*THYROID FUNCTION TEST

Thyroid function test is commonly employed to assess the hormonal status of HT by assessing the levels of thyroid stimulating hormone (TSH), tri iodothyronine(T3), tetra iodothyronine (T4).among these TSH is the sensitive marker of hypothyroidism and diagnosis of subclinical hypothyroidism. Frequent monitoring of TSH is needed to assess the response of the treatment and disease progression.[7]

*ULTRASONOGRAPHY:

USG shows focal or diffuse glandular enlargement with coarse, heterogenous and hypo echoic pattern. Presence of discrete hypo echoic micro nodules (1 to 6 mm) is strongly suggestive of chronic thyroiditis. Fine echogenic fibrous septa may produce pseudolobulated appearance.

Colour Doppler shows extensive hypervascularity.
Variations in presentation of Hashimotos:

Small atrophic gland may be present at end stage of disease.

Nodular form may be present in background of diffuse thyroiditis.

Benign and malignant nodules may coexist in the background of diffuse thyroiditis. FNAC is needed to differentiate them.

Grade 3 correlates with raised anti TPO and TSH[25]

Ultrasound neck showing Hypoechoic areas

*FNAC:

FNAC smears are characterized by the cellular aspirate with numerous dispersed heterogenous lymphocytes and few follicular cells. Based on the degree of lymphocytic infiltration the cytology of HT is graded as follows:

FIGURE:5 FNAC shows abundant lymphocytes with few thyroid follicles and Hurthle cells

THYROIDITIS DIFFERENTIAL DIAGNOSIS

1. Subacute granulomatous thyroiditis- a self limiting painful disorder of thyroid. clinical examination, elevated ESR, elevated thyroglobulin level and decreased radioactive iodine uptake confirms the diagnosis.

2. Acute suppurative thyroiditis- Is a rare infectious condition of thyroid.

3. Reidel’s thyroiditis is fibrous disorder of thyroid characterized by hypothyroidism and hypocalcemia and diagnosis is made by histopathology. Glucocorticoid is the mainstay of treatment.
ASSOCIATIONS:

Papillary carcinoma thyroid (PTC):

There is a well established association between HT and papillary carcinoma thyroid. PTC with HT is characterized by female predominance (30% more likely to have co existing PTC), multifocality, no extrathyroid extension, no lymphnode metastasis and better recurrence free survival.[14][17][26]

MALTOMA

Rapid non tender enlargement of thyroid gland in HT should raise the suspicion of Lymphoma. It is very difficult to differentiate reactive and neoplastic changes in cytology. Flow cytometry, immune histochemistry or PCR should aid in diagnosis.[20][21]

Other autoimmune diseases like Addison’s disease, diabetes mellitus type 1, rheumatoid arthritis, systemic lupus erythmatosus or viteligo can coexist with HT.

MANAGEMENT:

Treatment of Hashimoto thyroiditis is mainly medical. Supplementing L-thyroxin for hypothyroidism. L-thyroxin has proved to reduce the volume of thyroid in both hypothyroidism and even euthyroid. The dose of L-thyroxine is tailored according to the patients need. The standard dosage is 1.6-1.8 mcg/kg /day. The level of TSH is frequently monitored for dose adjustment till euthyroid state is attained thereafter every 6-12 months.

Some case of spontaneous recovery in HT has been reported.[19] When levothyroxine and selenomethionine are given together its found to reduce the release of cytokines from monocytes and lymphocytes thus reducing the thyroid peroxidase antibody titre and autoimmune process in HT.[23][24]

Surgery is generally avoided in HT as it is unnecessary to induce hypothyroidism. Thyroidectomy is considered in patients with cosmetic problem, with compressive symptoms (like dysphagia, dyspnea, change of voice) suspicion of malignancy as papillary thyroid carcinoma is commonly associated. surgery has some beneficial effect on painful thyroiditis[18]. Radioactive iodine treatment can be considered as a last option in elderly patients with large goiter in whom thyroiditis is not responding to levothyroxine and refusing surgery.[16]

CONCLUSION:

So a case presenting with goiter and features of hypothyroidism, there is higher possibility of Hashimoto’s thyroiditis which can be even euthyroid or hypothyroid. Unnecessary surgical intervention should be avoided to prevent permanent hypothyroidism. We should search for other associated autoimmune conditions, do cytological examination in nodular goiter to rule out associated thyroid malignancies. Regular monitoring of thyroid function test is mandatory to assess the disease progress and titrating the dose of levothyroxine
References:

1. Hashimoto’s Thyroiditis: History and Future Outlook

Yuji Hiromatsu,1 Hiroshi Satoh,2 Nobuyuki Ami-no3

1Division of Endocrinology and Metabolism, Kurume University School of Medicine, Kurume, 2Division of Surgery, Kyushu University and Japanese Society for the Medical History, Itoshima, Fukuoka, 3Kuma Hospital, Center for Excellence in Thyroid Care, Chuo-ku, Kobe, Japan

2. Hashimoto’s Thyroiditis: From Genes to the Disease Katja Zaletel and Simona Gaberek*

Department of Nuclear Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia, Current Genomics, 2011, 12, 576-588

3. IMMUNOGENESIS OF HASHIMOTO’S THYROIDITIS Dimitry A Chistiakov, laboratory of Aquatic Ecology, Katholeke Universiteit leuven, Ch. De Beriotstraat 32 B- 3000, Belgium

4. Immune Disorders in Hashimoto’s Thyroiditis: What Do We Know So Far?

Aleksandra Pyzik,1 Ewelina Grywalska,2 Beata Matyjaszek-Matuszek,1 and Jacek Roliński2

Hindawi Publishing Corporation Journal of Immunology Research Volume 2015, Article ID 979167, 8 pages

5. Hashimoto’s Thyroiditis: Countrywide Screening of Goitrous Healthy Young Girls in Postiodization Phase in India. R. K. MARWAHA, NIKHIL TANDON, A. K. KARAK, NANDITA GUPTA, KUSUM VERMA, AND N. KOCHUPILLAI Departments of Endocrinology and Metabolism (R.K.M., N.T., N.G., N.K.) and Pathology (A.K.K., K.V.), All India Institute of Medical Sciences, New Delhi, India

6. Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a pre-clinical state. Staii et al. Thyroid Research 2010, 3:11 http://www.thyroidresearchjournal.com/content/3/1/11

7. Hashimoto’s Thyroiditis

Arvin Parvathaneni, Daniel Fischman and Pramil Cheriyath Pinnacle Health System-Harrisburg Hospital Harrisburg, Pennsylvania, USA


9. The Immunopathogenesis of Chronic Autoimmune Thyroiditis One Century after Hashimoto

Anthony P. Weetman Department of Human Metabolism, Faculty of Medicine, Dentistry and Health, University of Sheffield, Sheffield, UK

12. Hashimoto’s disease - from theory to practice Syrenicz Thyroid Research 2013, 6(Suppl 2):A60


15. Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a pre-clinical state. © 2010 Staii et al Endocrinology, Diabetes and Metabolism, Department of Medicine, School of Medicine and Veterans Affairs Medical Center, University of Wisconsin- Madison, Madison WI 53792, USA


17. Hashimoto’s thyroiditis is associated with papillary thyroid carcinoma: role of TSH and treatment with L-thyroxine. Fiore et al Endocrine-Related Cancer (2011) 18 429–437


20. Maltoma of the Thyroid in a Man with Hashimoto’s Thyroiditis- WOZNIAK ET AL Vol. 84, No. 4,1999 The Journal of Clinical Endocrinology & Metabolism


23. Levothyroxine Treatment Reduces Thyroid Size in Children and Adolescents with Chronic Autoimmune Thyroiditis


24. The Effect of Levothyroxine and Selenomethionine on Lymphocyte and Monocyte Cytokine Release in Women with Hashimoto’s Thyroiditis

Robert Krysiak and Boguslaw Okopien (J Clin Endocrinol Metab 96: 2206–2215, 2011)