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Hashimoto's thyroiditis

Ewa Machała^{1,a}, Magdalena Redynk^{1,b}, Iulia Iavorska^{2,c}, Piotr Machała^{3,d}

¹ Department of Endocrine, General and Oncological Surgery,
Medical University in Lodz, Lodz, Poland

² Department of Hematology, Kopernik Memorial Hospital in Lodz, Lodz, Poland

³ Institute of Catholic Philosophy, Faculty of History of Philosophy,
Pontificia Facultas Theologica Wratislaviensis, Wroclaw, Poland

^{a-d}E-mail address: ewamachala@o2.pl , magdalena.redynk@gmail.com ,
julia_yavorska@yahoo.com , pepeuk13@poczta.fm

ABSTRACT

Chronic lymphocytic thyroiditis also known as Hashimoto's disease is an autoimmune disease in which the body's immune system attacks own cells of organism and destroys thyroid gland. More precisely lymphocytes accumulates in thyroid. It leads to inflammation and disturbance in its ability to producing hormones. Effects of disease include painless, diffuse enlargement of gland, replacing of parenchyma by a lymphocytic infiltrate and fibrotic reactions- some kind of follicles can be also found. Thyroiditis cause to lose abilities to store iodine by gland. Its lower level of iodoproteins and in turn level of hormones. Increased TSH production and stimulation occurs. Occurrence of diffuse firm goiter (especially in women) in euthyroid or hypothyroid state, increased levels of TG Ab and TPO Ab- this can be strong argument to put diagnosis. Significant morbidity is severe problem of health care system. Genetic and environmental factors are responsible for causation of thyroiditis. In some cases for example large goiter, fast growth, hypothyroidism there is indication for hormonotherapy. In special cases surgery consideration of surgery in needed. The etiological factors of disease are discussed. Our focus is on the presentation of disease, pathophysiology and diagnostic difficulties with analysis of modern literature.

Keywords: chronic lymphocytic thyroiditis, Hashimoto's thyroiditis, Hashimoto's disease, goiter, hypothyroidism

1. INTRODUCTION

In the beginning of 20th century dr. Hakaru Hashimoto described state of four patients-women in middle age- with still unknown chronic disorder- named “struma lymphomatosa”. Thyroidectomies were performed for patients due to compression signs (pain in neck, dysphagia, odynophagia, dyspnea) of large goiter. After this histopathological examination of obtained material of thyroids were performed.

Microscopic photos of specimens of thyroid were published. He concluded that glands in this condition were diffusely infiltrated by lymphocytes, fibrosed with parenchymal atrophy, eosinophically changed [1]. He compared a new disease entity named as “Hashimoto’s thyroiditis” to Mikulich’s disease (yet know as Sjogren’s syndrom) but with counting of differences.

After this process changing of nomenclature didn’t appear- still such conditions was associated with Riedl’s thyroiditis. In 1931 Allen Graham postulated and proved that struma lymphomatosa described before by Hashimoto, should be classified as an autonomic disease. From this time of publication disease started to be called in English language as Hashimoto’s thyroiditis.

First case of diagnosed thyroiditis was described in John Hopkins Hospital in Baltimore in 1942- this means almost 30 years after Hashimoto’s thesis.

Many researches and studies were dedicated to solve basic questions, problems of so widespread condition. Officially disease was called: Hashimoto’s thyroiditis, lymphocytic thyroiditis, chronic thyroiditis, autoimmune thyroiditis. We can observe that almost in all descriptions word “thyroiditis” plays crucial role. Detected by Fromm et al. in 1953 plasma gamma globulin “proved” that this disease is associated with immunologic abnormalities [2]. Next authors of very influential study put thesis that the disease might be related to a long-lasting continued autoimmune reaction [3].

Finally due to experiments on rabbits Rose and Witebsky found antithyroglobulin antibodies in the blood of animals [4]. In 1956 Deborah Doniach from London concluded that patients with this disease have developed immunological reaction for human thyreoglobulin. Roitt et al. proved that serum antibodies are responsible for disease development [5]. The disease was associated with young women with diffused enlargement of the thyroid gland in euthyroid or often hypothyroid state. In 1985 published information about identification of human thyroid peroxidase (TPO)- protein, autoantigen of antibodies a/ TPO.

Because of needle aspiration biopsy, serological tests much more common recognition of Hashimoto’s thyroiditis is observed. But till now it is still enigmatic disease with not so well known causes and etiology.

With increase in incidence, thyroiditis has been associated with other disorders such as diabetes mellitus, rheumatoid arthritis, celiac disease, multiple sclerosis, vitiligo. There is data about coexistence of papillary carcinoma of thyroid with Hashimoto’s disease.

Hashimoto’s thyroiditis is more frequent in women than in men. According to P. Carturegli et al. incidence of disease is at least 8 times higher in women than in men [6]. But according to study positive results of laboratory test in women for occurrence of antibodies for thyroid appear in almost 10% of population [7].

In article we focused on the presentation of disease, relation with other autoimmune diseases, etiology, pathophysiological changes, diagnostic modalities, treatment strategies.

2. EPIDEMIOLOGY

Hashimoto's thyroiditis may occur at any age- stage of life but it is most often observed in women between 30 and 60 years old [8]. Exact incidence of disease is unknown but can be similar to incidence of Grave's disease. Due to investigations its more common in regions of high iodine intake and especially with genetical predispositions. It is one of the most common causes of primary hypothyroidism, non- endemic goiter.

The determinations of exact incidence and prevalence rates its problematic because of variable expressions of disease in different regions. Hashimoto's thyroiditis is more frequent in women than in men. According to P. Carturegli et al. incidence of disease is at least 8 times higher in women than in men [6]. But according to other study positive results of laboratory test in women for occurrence of antibodies for thyroid appear in almost 10% of population [7]. According to Yurji Hiromatsu prevalence in all age groups is around 2%, year incidence 0.3-1.5/ 1000 people per year [7].

Clinically proved hypothyreosis in Hashimoto's disease occurs around in 1-3% of cases. One of the most interesting investigations was held in Whickham- Great Britain in Tyne and Wear region. In women population they observed 1.9-2.7 % cases of hyperthyreosis, 1.9% hypothyreosis. In 7.5% of woman found elevated levels of thyreotropine (TSH), 10.3 % positive test for presence of anti- thyroid peroxidise antibodies (aTPO). Presence of goitre was diagnosed in 15% of women. In diagnosed men population abnormalities was 4-10 fold less frequent [9].

It is very important that studies employing ultrasound guided biopsy, cytological and serological examination have recorded higher prevalence than other studies.

Familiar predisposition is known. Many of persons without clinical signs have aTG and aTPO antibodies. Some authors suggested a potential role for skewed X chromosome activation- as an explanation for female predominance in common thyroid autoimmune diseases, Grave's disease, Hashimoto's thyroiditis [10].

3. ETIOLOGY

The etiology of Hashimoto's disease is multifactorial but till now not directly known. Aspects such as genetic, immunological, environmental factors can play main role in its development. Other authors suggest that this is cooperation of genetic, epigenetic and environmental factors. Genetic predisposition to Hashimoto's thyroiditis is proved nowadays but there is still many difficulties with determination of importance of each gene involved in pathophysiology of disease.

Human leukocyte antigen is associated with development of auto-immunological diseases also in Hashimoto's thyroiditis. The disease is associated with CTLA-4 – cytotoxic T- lymphocyte antigen, major histocompatibility complex (MHC) - genetic factors. CTLA-4 transmits an inhibitory signals to T cells which in turn increase T- lymphocyte activity [11]. Familiar predisposition of disease is associated with HLA- DR5 gene [12]. External factors such as infections, cytokine therapy, selenium and iodine intake also play important role in the etiology of disease especially in individuals with genetic predispositions.

Other immunological diseases can trigger development of Hashimoto's disease- but opposite way of action is also possible.

Some of ethnic groups can predispose to development of disease. The risk of its development is also higher in people with chromosomal disorders including:

- Turner syndrome
- Down syndrome
- Klinefelter syndrome.

In case of chromosomal abnormalities production of autoantibodies against thyroglobulin and thyroperoxidase occurs.

The main causes of development of Hashimoto's thyroiditis are counted in Table 1.

Table 1. Causes of Hashimoto's thyroiditis

Causes of Hashimoto's thyroiditis	
1.	Genetical predisposition
2.	Hormones
3.	Excessive iodine
4.	Radiation exposure
5.	Heavy metals toxicity
6.	Insuline resistance
7.	Gluten, Food sensitiveness
8.	Vitami D Receptor polymorphism
9.	Cigarette smoke
10.	Postpartum
INFECTIONS:	
11.	Epstein- Barr virus
12.	Yersinia enterocolica
13.	Herpes
14.	Lyme disease
15.	Cytomegalovirus
16.	Q fever
17.	Rubella/ Rubeola

18.	Staphylococcus, streptococcus infections
19.	Rickettsia
20.	Coxsackie
21.	Helicobacter pylori
22.	Parvovirus B19
23.	Hepatitis C
24.	HTLV-1
25.	HIV
26.	Enterovirus
27.	Flu virus

4. PATHOGENESIS

In most simply explanation disturbances in immune tolerance to thyroid cells causes production of antibodies against thyroid cells. This process results in destruction of tissues of this gland. When genetically predisposed individual are exposed to risk factors process mention above begin. There are multiple main theories of pathology of its development with is characterized by lymphoid infiltration of gland including T and B cells. In pathogenic mechanism take a role both cellular and humoral immunity. Possible pathogenic pathways is summarized in Figure 1.

Dendritic cells and macrophages- components of major histocompatibility complex class 2 antigen presenting cells- due to inflammatory process migrate to thyroid gland. They are able to present autoantigen components of gland to immune system cells [21]. According to some publications thyroglobulin plays main role in development of these disease [22]. They ability of having approximately 40 different epitopes triggers immune and inflammatory processes [21]. Some enzymes- for example thyroid peroxidase that catalyzes the oxidation of iodine can play role of autoantigen.

Production of reactive cells and autoantibodies in response to presented antigens occurs in the lymph nodes but in case of progression of disease in the thyroid gland. The development of lymphoid tissue follows. Overstimulated B- lymphocytes produce antithyroglobulin and antithyroid peroxidase antibodies and initiate the process of tissues destruction [21].

During the development of disease the control over destruction of cells of thyroid is disturbed. Causes of this deregulation are connected with genetics, expression of Bcl-2, FasL membrane proteins [21].

In autoimmune thyroid disorders from peripheral space T-cells migrate inside thyroid tissues. Failure of antigen- specific T suppressor implicating in disease development [13]. Regulatory T- cells are be also involved in autoimmune thyroid disease development

[14-16]. Possible mechanism of development of disease is decreasing sensitivity of CD4+ T cells to inhibition by TGFβ [17].

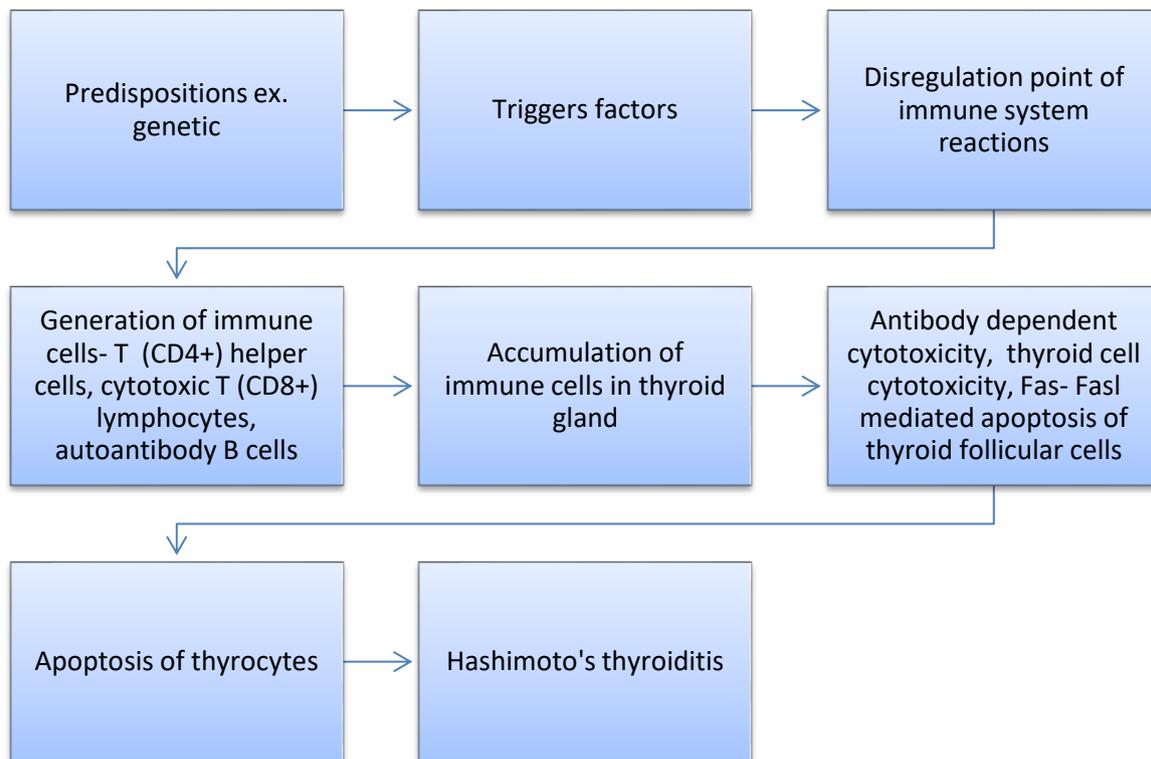


Figure 1. Pathogenic pathways of Hashimoto's thyroiditis

Increased number of follicular helper T cells has been shown in peripheral blood in patients with Hashimoto's disease. They are involved in promoting antigen specific B cells and production of IL-21. Follicular helper T cells plays important role in expressing chemokine receptor CXCR5 with inducible costimulator protein [18].

Cytotoxicity and apoptosis are causes of destruction of thyroid tissues in autoimmunological diseases. Such cells as CD8+T cells against TPO and TG are involved in process of cytotoxicity. Cytokines are responsible of disruption of synthesis of thyroid hormones and mediation in apoptotic process in cells through oxidation [20]. Apoptosis can be explained through increase expression of the apoptotic molecule, detection of apoptotic cell markers in samples [15, 19].

The main feature of Hashimoto's thyroiditis is thyroid specific antibody production-antibodies against TG and TPO. Recently are documented that IgG4- causing sclerosis, that infiltrate gland are combined with development of some types thyroiditis [23].

Antibodies against thyroid stimulating hormone receptor – thyroid stimulating antibodies and thyroid blocking antibodies takes part in regulation of hormones production during disease.

Antibodies involved in Hashimoto's tyroiditis are counted in Figure 2.

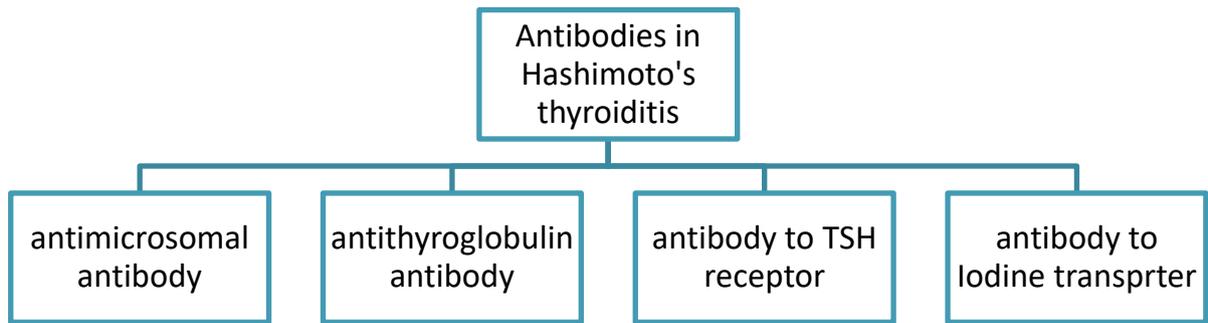


Figure 2. Antibodies in Hashimoto's thyroiditis

5. PATHOMORPHOLOGY

On pathologic examination can be observed diffuse lymphocytic infiltrations composed from T and B- cells with germinal centers [24]. Nuclear clearing its a common morphological feature, oncocytic metaplasia may be present or not. Enlargement of gland can be symmetrical or asymmetric due to progression of disease. Changes are accompanied by destruction of thyrocytes and destruction of proper structure of follicles, atrophy even with interlobular fibrosis. The capsule often is intact with prominent pyramidal lobe. Such changes as necrosis and calcification can suggest a different diagnosis. Structure of glandular tissues is similar to lymphatic nodules.

6. SIGNS AND SYMPTOMS. DIAGNOSIS OF HASHIMOTO'S THYROIDITIS

Thyroid hormones can influence on function of every cell in the body. They regulate the basal metabolism rate of the body. Decreased production of thyroid hormone is connected with destruction of gland tissue and in turn in decreased metabolic rate. Symptoms of Hashimoto's thyroiditis manifests in advanced stage of disease. Hypothyroidism affects almost all major organs. Thyroid hormones regulation is illustrated in Figure 3.

Wiersinga and colleagues in article identified 5 stages of Hashimoto's.

The course of Hashimoto's thyroiditis can be divided into 5 stages of the disease [25, 26]:

1) First stage also known as Stage 0 / GENETIC PREDISPOSITION

- Genetic predisposition but still not exposition to triggers
- Normal serum levels of FT3, FT4, TSH
- Lack of clinical symptoms

2) Second stage// IMMUNE CELL INFILTRATION OF THYROID GLAND

- Increased levels of thyroid autoantibodies- anti- TPO, anti- TG but forms of serum negative Hashimoto's thyroiditis can be present
- Normal levels of FT3, FT4, TSH
- Symptoms such as anxiety, fatigue, infertility, mood, swings, excess weight, weight loss

- can be manifested. Non symptomatic stage also can appear
- Specific changes in Ultrasound and Cytological examination
 - Immune activation in form of migration and clustering of macrophages, dendritic cells
 - Destruction of thyroid parenchyma triggers release of excess of thyroid hormones- intermittent event of thyrotoxicosis can appear (with presence of antibodies stimulating receptor- TSH)
 - More often signs of subclinical hyperthyroidism can be observed

3) Third stage- SUBCLINICAL HYPOTHYROIDISM

- Elevation of serum TSH
- Normal range of FT3, FT4
- Increase in level of thyroid antibodies or without changes in serum negative form of disease
- Individual occurrence and severity of clinical symptoms

4) Fourth stage- OVERT HYPOTHYROIDISM

- Thyroid gland failure
- Primary hypothyroidism
- Elevated TSH levels, low levels FT3, FT4
- High thyroid antibodies
- Required thyroid medications
- Presence of clinical symptoms
- Reduction in the concentration of at least one thyroid hormone

5) Fifth stage- PROGRESSION OF OTHER AUTOIMMUNE DISORDERS

- High risk of developing other autoimmune diseases as celiac disease, psoriasis, Sjogren's disease, rheumatoid arthritis, multiple sclerosis etc.
- High imbalance in immune system tends it to attack other body tissues- small intestine, salivary, tear glands, joints etc.
- In some cases recommended thyroidectomy

The decreased level of thyroid hormone can affect almost all system and organs. In Hashimoto's thyroiditis such symptoms as: bradycardia, constipation, delayed reflexes, increased bile reflux. Disease is often misdiagnosed with depression, PMS, chronic fatigue, fibromyalgia, anxiety disorder. Results of laboratory examinations: TSH, FT3, FT4 and anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies, anti-microsomal antibodies are main diagnostic points- gold standards.

In ultrasonography thyroid volume maybe proper or increased. But in most cases due to course of disease- atrophic changes and fibrosis with infiltration can appear even decrease size of thyroid gland. We can distinguish different variants of disease tendency in different age groups. In older women- more characteristic is fibrous changes and rapid progression of hypothyroidism. In younger patients periods of remission and relapses prevail.

There is possible three variants of clinical presentation in Hashimoto's thyroiditis: hypothyroid, euthyroid, hyperthyroid. Around 20% of the patients can represent signs of mild hypothyroidism [21]. Increase in the severity of symptoms is associated with progression of disease such as gradual destruction of thyroid gland [21].

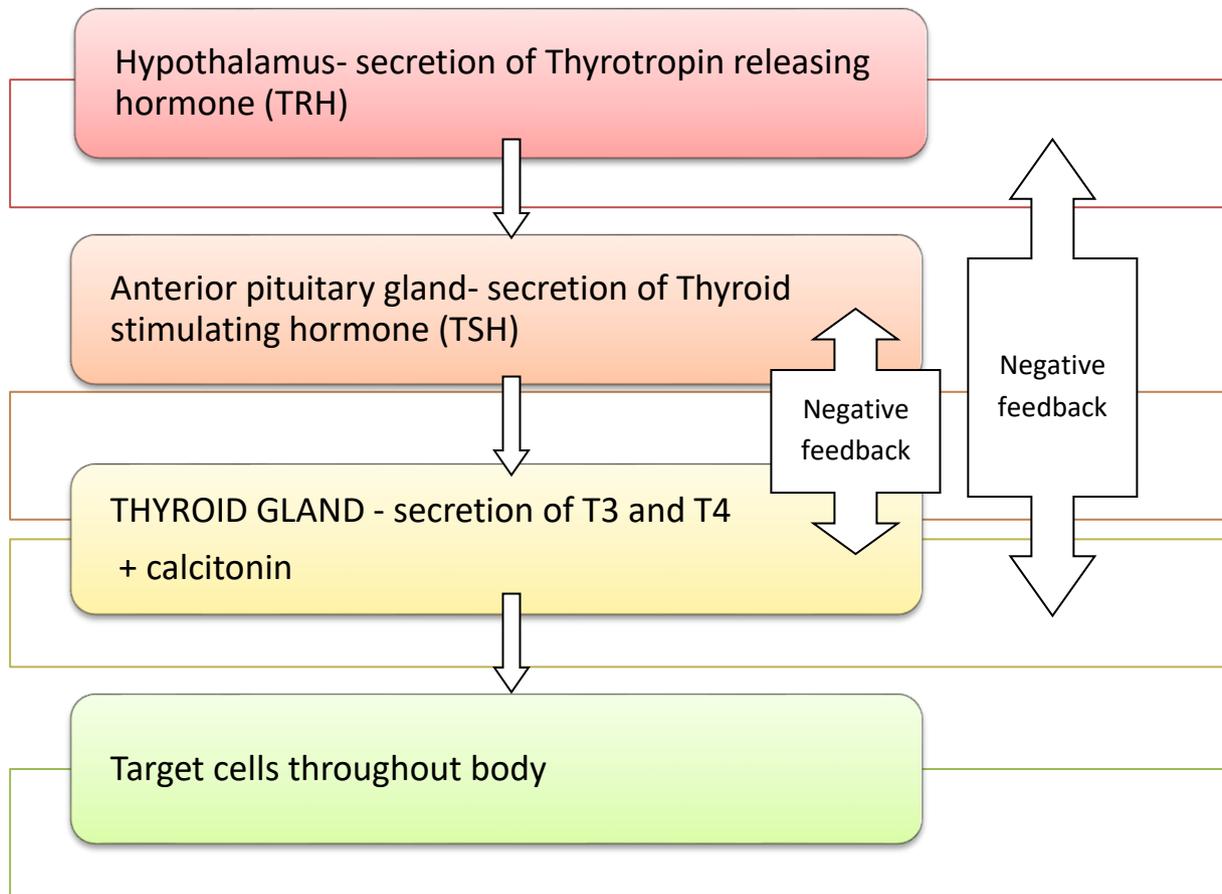


Figure 3. Thyroid hormones regulation

Typical signs and symptoms of Hashimoto’s thyroiditis are presented in Table 2.

Table 2. Signs and symptoms of Hashimoto’s thyroiditis

MAIN SIGNS AND SYMPTOMS OF HASHIMOTO’S THYROIDITIS	
<ul style="list-style-type: none"> - fatigue and weakness - dry skin - coarse skin - depression - cold intolerance - dyspnea - weight gain - cognitive dysfunction - constipation - bradycardia 	<ul style="list-style-type: none"> - delay of reflexes - hoarseness - edema, periorbital edema - puffy facies and eyelids - enlargement of tongue - myalgia, paresthesia - menorrhagia - pubertal delay - galactorrhea - mental retardation (infants)

Hypothyroidism secondary to Hashimoto's disease can be reversible condition. According to long observations- studies revealed a decrease in level of thyroid antibodies in patients treated with thyroid hormone and regularly monitored with proper management of disease [27]. It is known well association of Hashimoto's disease with autoimmune diseases. Still there is controversial question about connections of disease with cancer development. According to investigation the incidence of thyroid carcinoma in patients with Hashimoto's thyroiditis is equal 36.4% [28]. Lymphoma and papillary carcinoma of thyroid gland prevail in investigation. One of the largest scale nationwide cohort study of cancer and Hashimoto's thyroiditis was conducted on Asian population- in Taiwan. Due to results of study patients with Hashimoto's thyroiditis- especially older patients- are at higher risk of developing thyroid and colorectal cancer compared with population [29]. According to other article in which they analyse results of 36 studies -64 628 subjects- published between 1955-2016 from 13 counties they found relative risk of Hashimoto's thyroiditis among papillary cancer cases- 2, 36, an relative risk of papillary carcinoma in cases of Hashimoto's thyroiditis 1,40 and a relative risk of thyroid lymphoma among Hashimoto's thyroiditis patients equal 9,74. So they conclude that there is association between Hashimoto's thyroiditis - papillary carcinoma and Hashimoto's thyroiditis - thyroid lymphoma [30].

Changes in the thyroid gland may start long before the symptoms of hormonal imbalances. Finally they can manifest when the process of disease will be advanced. Screening of people for Hashimoto's through antibody testing and ultrasound studies should be obligatory. Early detection of the disease will help a patient prevent a myriad of unpleasant symptoms. Out of the thyroid autoantibodies, anti-TPO and anti-TG levels should be routinely determined, the increase of which is the most typical laboratory sign for the disease. Anti-TPO autoantibodies are most frequently elevated. In the case of normal level of anti- TPO antibodies, anti-TG levels should also be determined. It is postulated that the production of autoantibodies against thyroglobulin is more characteristic of the initial period of disease, while the production of autoantibodies against thyroid peroxidase occurs in more advanced stages of disease [31]. Ultrasound examination can prove development of Hashimoto's disease. A typical ultrasound image in advanced disease includes lowering the echogenicity of thyroid parenchyma to a level comparable to the echogenicity of adjacent muscles due to replacement of normal structure of the parenchyma with lymphocytic infiltrates. Depending on the degree of fibrosis of thyroid parenchyma we can observe various intensified heterogeneity of echogenicity, associated with the presence of deposits of collagen fibers. Doppler ultrasound indicates an increase in vascular flow in the thyroid gland, especially in cases of hypothyroid patients. Reactive enlargement of regional lymph nodes can be observed [32]. Fine-needle aspiration biopsy is not considered as a routine examination in patients with Hashimoto's thyroiditis. If its performed according to indications cytological image is dominated by small mature lymphocytes, activated lymphocytes, plasmocytes and oncocytes (Hürtl cells) [33].

7. CONCLUSIONS

In this article we have discusses epidemiology, pathogenesis and pathology of Hashimoto's thyroiditis. We have also discussed potential signs and symptoms of disease and indicated ways of diagnosis. There is no effective treatment for Hashimoto's patients. The therapy is primarily based on treatment of the effects of disease or treatment of hypothyroidism.

Systematic thyroid tests such as blood test and ultrasonography are indicated regularly. The key drug in treatment is levothyroxine which has similar properties to thyroid hormone and is used as substitution therapy for hypothyroidism.

If Hashimoto's thyroiditis is treated properly it does not cause complications. Rare thyroid changes such as thyroid lymphoma or papillary thyroid carcinoma are observed. This are examples of how aggressive can be immune system. That's why we need to understand and investigate, study more about predispositions and pathophysiology of disease. Nowadays exist also very important questions about environmental and infectious impact on development of Hashimoto's thyroiditis.

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