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University of Nevada, Reno

A Clinical Analysis and Review of Literature Associated with Hashimoto's Thyroiditis

A thesis submitted in partial fulfillment
Of the requirements for the degree of

BACHELOR OF SCIENCE IN BIOCHEMISTRY

by

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May, 2012

**UNIVERSITY
OF NEVADA
RENO**

THE HONORS PROGRAM

We recommend that the thesis
prepared under our supervision by

JACOB SORENSEN

entitled

A Clinical Analysis and Review of Literature Associated with Hashimoto's Thyroiditis

be accepted in partial fulfillment of the
requirements for the degree of

BACHELOR OF SCIENCE, BIOCHEMISTRY

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Abstract:

Hashimoto's thyroiditis (HT), named after its discoverer Hakaru Hashimoto, is a chronic autoimmune inflammatory disease. HT develops when an autoimmune response causes inflammation of the thyroid gland that ultimately leads to the destruction of thyroid tissue, effectively killing the organ. An affected patient may simply be asymptomatic during the initial phases or he or she can present with many vague underlying symptoms due to the broad range of thyroid hormones functions, including mood and appetite regulation (Tomer and Huber 233). However, serious complications such as myxedema coma, Hashimoto's encephalopathy, and even thyroid cancer can occur. While a very effective hormone replacement therapy exists, there is still no cure that can reverse or halt the damage caused by Hashimoto's thyroiditis. The research for this thesis will be gathered from academic papers and medical literature documenting the condition.

This thesis was written to condense and organize the medical and research community's collective knowledge of Hashimoto's thyroiditis. Also included, is the outline of a case study based loosely on a real patient treated while I was shadowing an internist in Elko, Nevada. The case study includes lab findings and treatment details. Discussed in the thesis will be in-depth information regarding the pathology of HT and the treatment options for the present and near future. Overall, this thesis is meant to cover everything a practicing physician would need to know to effectively treat HT and it also delves into the cutting edge research being conducted by experts worldwide.

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Introduction to the Condition

Globally, Hashimoto's thyroiditis has an average occurrence of 1.5 cases per 1000. Hashimoto's thyroiditis or HT presents in women up to ten times more than it does in men, with the likelihood of presentation peaking between ages thirty and sixty-five. HT is thought to be passed down genetically and there is evidence supporting that a mutation in the HLA-DR5 gene is at least partially responsible for disease pathogenesis (Kavvoura 3163). HT may progress so slowly that patients may not develop symptoms for months or years after the immune system begins attacking. Eventually, a patient will develop hypothyroidism. Hypothyroidism is characterized by a loss of function of thyroid gland and normal thyroid hormone secretion which, as discussed next, has adverse effects on the body. Often the onset is sudden, and more rarely it is preceded by a bout of hyperthyroidism. Hyperthyroidism is effectively the opposite physiological ailment to that of hypothyroidism. The abnormal inflammation of the thyroid can cause the counterintuitive effect of temporarily but drastically increasing thyroid hormone secretion. Hashimoto's begins when, for unknown reasons, a cell and anti-body mediated immune response start specifically targeting the thyroid gland and more specifically the thyrocytes (thyroid cells). Antibodies for thyroid peroxidase and thyroglobulin begin attacking and destroying follicles in the thyroid causing normal thyroid cells to form into modified Hurthle cells. The long arrow in Figure 1 indicates a thyroid cell that has ruptured into a type of Hurthle cell. Helper T-Lymphocytes (a type of Leukocyte) also play a part in the destruction by targeting the thyroid tissue for destruction by other immune response elements such as cytotoxic cytokines and macrophages (Kumar 1213). As the thyroid cells become compromised, symptoms of hypothyroidism start to appear. An incomplete list of common symptoms include: weight gain, depression, sensitivity to heat and cold, fatigue, panic attacks, bradycardia, and high cholesterol (Fava, Oliverio, and Guiliano 525).

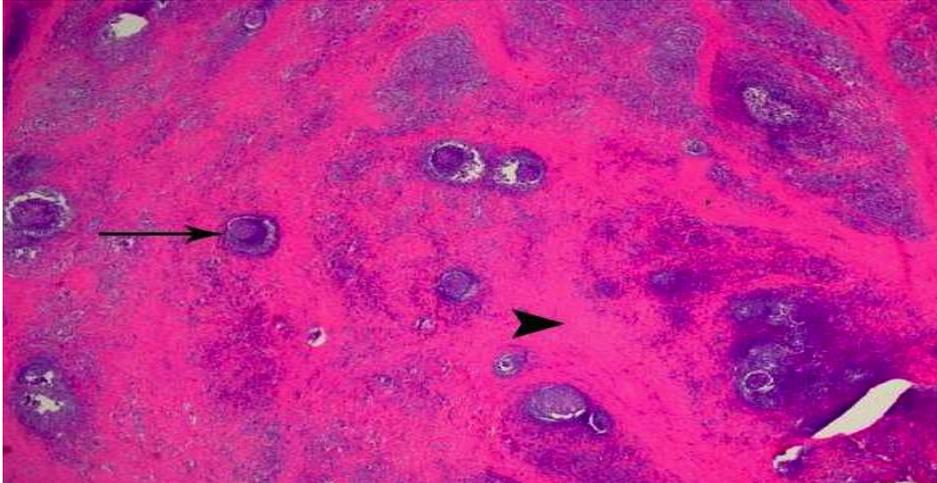


Figure 1: **Thyroid Hurthle cells** (indicated by long arrow) (Mcmanus et al. 52)

The thyroid is a large endocrine gland located below the laryngeal prominence or Adams apple. The endocrine system refers collectively to a system of glands that secrete hormones directly into the bloodstream. Inflammation of the thyroid due to HT can cause fibrosis or excessive formation of connective tissue leading to scarring. This often leads to a goiter or a physically enlarged thyroid. To preserve homeostasis, the hypothalamus releases TRH (thyrotropin-releasing hormone) to the anterior pituitary gland, which regulates the release of TSH (thyroid stimulating hormone) which will elicit a response from the thyroid. The thyroid is responsible for the production of triiodothyronin (T3) and thyroxine (T4) hormones as well as calcitonin (Ben-Skowronek et al. 340). These hormones have important roles in the rate of metabolism as well in regulating the sensitivity of the body to other endocrine hormones. As the thyroid starts to deteriorate from the anti-bodies turning healthy thyroid cells into nonfunctioning Hurthle cells, the gland is no longer able to synthesize and release these regulating hormones. The hypothalamus will attempt to compensate by releasing more TRH which will in turn cause a release TSH from the pituitary gland. However, the damaged thyroid will fail to respond and

more TSH will be secreted into the bloodstream. An elevated serum TSH level is the first clinical indicator of hypothyroidism and possible HT. Other possible causes for high TSH levels include iodine deficiency or thyroid cancer (McManus et al. 55).

Hashimoto's is treated with hormone replacement therapy in which a patient ingests a synthetic hormone as a substitute for the missing thyroid ones. A doctor decides the amount based on weight, sex and severity of the disease and monitors blood levels of TSH until normal levels are reached (Tomer and Huber 335). This medication has no effect on the immune system however, and the thyroid is eventually completely destroyed. For other autoimmune disorders such as Rheumatoid arthritis there are drugs such as methotrexate that promote disease remission, but they have high risk of infection due to the weakening the immune system. As far as I have seen, these types of drugs are not used to treat HT as the hormone replacement therapy is safer and more effective.

Severe and prolonged hypothyroidism can also have rare complications such as myxedema coma. Extended hypothyroidism can cause myxedema which has the symptoms of mental slowness, weakness, and hypothermia. Myxedema can quickly lead to a Myxedema Coma which has a high mortality rate of around 30-40%. Hashimoto's encephalopathy is another very rare condition associated with Hashimoto's. It is a neuroendocrine disorder and up to 2005 only 200 cases had been reported (Berger, Castiel, and Dor 1903). Prolonged inflammation due to HT is known to correlate with papillary thyroid cancer, and in actuality only 1 in 5 of people who develop PTC present with HT symptoms (Ahn et al. 1231).

Historical background/social context

Hashimoto's thyroiditis was first described by Hakaru Hashimoto a Japanese Surgeon working in Germany during the early 19th century after post-operative studies. The incidence in the United States is put at 3.5 adult women per 1000 and 0.8 men per 1000 per year. The worldwide occurrence is estimated at 0.3-1.5 cases per 1000 people. Overall the likelihood of HT increases with age and peak incidence occurs at ages 30-65 years (Fava, Oliverio, and Guiliano 525).

Hashimoto's is the leading cause of hypothyroidism in first world countries with sufficient iodine supplies. Iodine is an essential component need for synthesizing thyroid hormones, and a deficiency can lead to an enlarged thyroid (goiter) and in extreme cases retardation or death. It is estimated that 29% of the world's population live in regions with danger of deficiency (Tomer and Huber 334).

The metabolic consequences of HT are receiving more attention as heart disease and obesity reach epidemic levels in the United States. Increased levels of Thyroid Stimulating Hormone (TSH) are known to be positively correlated with levels of LDL and HDL cholesterol along with triglyceride levels (Tagami et al. 255). Therefore, untreated Hypothyroidism will increase the risk of coronary artery disease, especially for those who are already at risk due to obesity or other lipid disorders. The risk for getting papillary thyroid carcinoma is also greatly increased in those with HT (Tagami et al. 256).

Hashimoto's also has the ability to initially cause temporary hyperthyroidism, the opposite of hypothyroidism, or over-activity of the thyroid gland. The symptoms are often opposite to those of hypothyroidism and include weight loss, palpitations, and sweating. Chronic hyperthyroidism is more likely caused by Grave's disease which is another auto-immune disorder of the thyroid.

With HT eventually the thyroid will be damaged by immune system and the patient will fall into hypothyroidism. This can cause drastic mood swings and can be misinterpreted as bi-polar disorder and/or depression. These mood disorders may not have immediate health risks, but they can have dramatic effects on the patient's social life, work, and relationships. As doctors become more used to treating mood disorders they may become less likely to search for a physiological reason behind them and resort to simply prescribing drugs such as anti-depressants. A timely diagnosis of HT requires the physician make a connection between the less tangible mood disorders and the physiological symptoms present.

Levothyroxine replacement therapy is the primary treatment and when monitored carefully by doctors is essentially a cure of symptoms. It allows the majority of patients to become asymptomatic and live normal lives. The treatment, however, is life-long, meaning it requires high patient compliance. This is often a major issue for doctors in the United States so it is important that doctors take the time to educate their patients of the risks involved. It would also benefit the patient to inform that they are at a heightened risk of heart disease, and likely one should advise health-promoting measures such as diet and exercise. Table 1 shows the relative frequencies of clinicopathological events that were presented within 36 months among people diagnosed with HT.

| Variables | Frequency |
|----------------------------------|-----------------|
| Period of study (months) | 36 |
| Period of follow-up (months) | 17.4 (6–36) |
| Mean age (years) | 41.3 (30–60) |
| Sex (F:M) | 31:3 |
| Nature of goiter | |
| -Diffuse | 14 |
| -STN | 11 |
| -MNG | 9 |
| Functional status | |
| -Euthyroid | 14 |
| -Subclinically hypothyroid | 6 |
| -Hypothyroid | 10 |
| -Hyperthyroid | 4 |
| Autoimmune association (n%) | 12 (35%) |
| Fnac findings | |
| -Hashimoto's thyroiditis | 11 |
| -Colloid nodule | 12 |
| -Malignancy | 3 |
| -Suspicious for malignancy | 2 |
| -Adenomatous goiter | 6 |
| Anti-TPO positivity ^a | 100% |
| TSH (mIU/L) | 3.9 (0.05–13.2) |

^a Anti-TPO titer was done only in 10 patients

Table 1: Clinicopathological pProfile of the HT cases: Events that precede thyroid removal

(Tomer and Huber 334).

Review of Literature

Hashimoto Thyroiditis, if diagnosed early, has largely been cured by development of a synthetic version of the T4 thyroid hormone. A dose that mimics what a healthy thyroid would produce is administered daily by the affected individual. This does not mean however that there is no need for further scientific research. The complex mechanisms that eventually result in the onset of Hashimoto's in healthy individuals are not well understood nor are the mechanisms of most autoimmune diseases. Hashimoto's has been observed to cluster with certain other serious autoimmune diseases. Insights into the mechanism of Hashimoto's could reveal valuable information in the pathophysiology of the other disorders that HT clusters with, and understanding these clusters will potentially reveal crucial information concerning all autoimmune diseases that debilitate and kill many otherwise healthy individuals.

Grave's disease is another autoimmune disorder affecting the thyroid. It causes the thyroid to become overactive and leads to hyperthyroidism. Hashimoto's and Grave's disease are often clumped together and collectively referred to as autoimmune thyroid disease (AITD) which is the most common subset of autoimmune disorders. Wiebolt in the Netherlands conducted a study in 2011 seeing how these two related disorders differed in their occurrence and their relative presence among other autoimmune diseases. Their studies showed that Hashimoto's is much more likely than Grave's disease to cluster with certain gastric autoimmunity disorders (5.3% in Hashimoto's compared to 1.2% in Graves). Also beta cell adrenal autoimmunity disorders clustered with Hashimoto's 3.2% of the time compared to 0.9 in Graves. Celiac disease did not seem to be correlated with either. This data shows that the characterization of AITD is not always sufficient when studying the occurrence of clustering of other autoimmune disorders.

The results also indicate that HT is the more likely of the two to associate with other disorders (Wiebolt 790).

Studies have also indicated that Hashimoto's has a strong genetic factor in which mutations in a certain gene greatly increase the risk that one will develop Hashimoto's. Many studies have linked the cytotoxic T-lymphocyte associated antigen gene known as the CTLA-4 gene. CTLA-4 is known as an inhibitor of T-lymphocytes which are the major perpetrators of thyroid destruction. On this gene there are two known mutations or polymorphisms that are known about: A49G and CT60. The analysis found that people with mutations in the G allele or the CT60 mutation had 1.4 fold increases in development of HT or Grave's disease. A49G relationships are less conclusive at this time (Kavvoura 3152). Figure 2 shows a comparison of the prevalence of the A49G and CT60 polymorphisms in HT found over several studies.

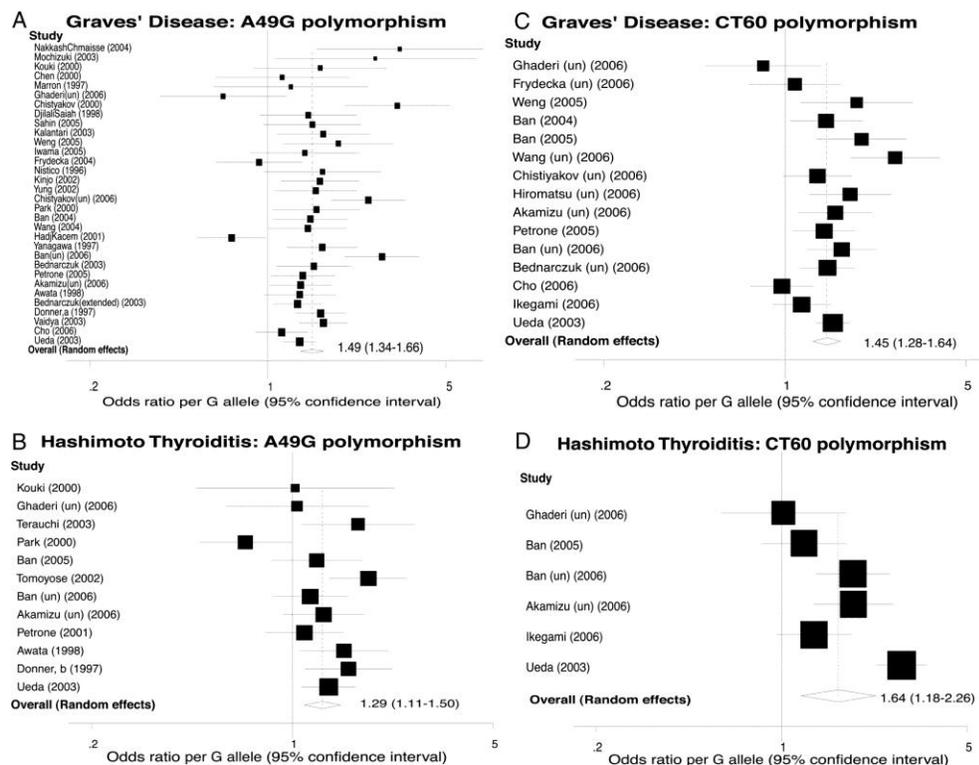


Figure 2: Polymorphism odds ratios: of HT development over several studies (Kavvoura 3169)

Normally hormone replacement therapy cures or alleviates symptoms of Hashimoto's enough for patients that no supplemental treatment is necessary. In some cases however, the inflammation of thyroid can cause anatomical problems such as tightness and difficulty swallowing amid other symptoms. For these patients there is the option of getting their thyroid surgically removed by a procedure known as a thyroidectomy. Surgeons in Wisconsin interviewed 1791 patients who underwent the procedure over four years to study the effectiveness of the surgery. They found that 93% of patients whose main pre-operative complaint was compression experienced a great improvement in symptoms. For voice problems or hormone imbalances 84% and 77% of patients respectively, were reported to have improved symptoms (McManus et al. 51).

There was another study that aimed to determine the specific auto-immune response cells that are responsible for the apoptosis or death of the cells of the thyroid. Researchers studied the cell samples taken from children with Hashimoto's and compared them with samples from children without an autoimmune disorder. The samples were inspected under an electron microscope for levels of specific receptors on cytotoxic T cells. Their studies found that present on the Hashimoto tissue samples were low levels of CD4 receptors compared to the normal tissue, while the level of CD8 receptors and also plasmocytes were much higher (Ben-Skowronek et al 336). This suggests that the CD8 receptors and plasmocytes are largely responsible for the immune mediated destruction of thyrocytes. These receptors were also studied across monozygotic twins and it was found that there was significant commonality of TPO epitope binding. Figure 3 shows a comparison of normal siblings versus monozygotic twin TPO epitope binding.

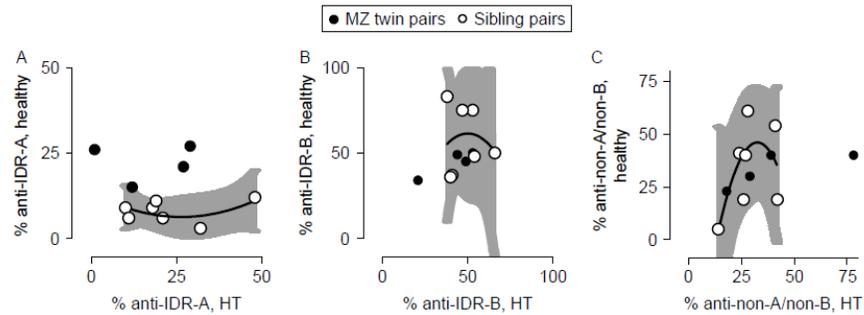


Figure 2. TPO autoantibody epitope recognition patterns within pairs discordant for HT. The percentage of TPOAbs recognizing the IDR-A (panel A), IDR-B (panel B), and non-A/non-B regions (panel C) within pairs of MZ twin pairs (●) and sibling pairs (○) is shown. Values for the subject with HT are shown on the *x*-axis and the values for the corresponding healthy co-twin/sibling are given on the *y*-axis. Ninety-five percent confidence intervals for the best-fitted curves are illustrated by the gray areas.

Figure 3: Twin epitope binding: patterns of epitope recognition between siblings and monozygotic twins suggesting that Hashimoto's is very likely passed down genetically (Ben-Skowronek et al. 341).

Chronic inflammation of a tissue has long thought to be a precursor for cancer of that tissue. Such a correlation is very evident between Hashimoto's and papillary thyroid cancer (PTC). Researchers in the study identified a 21.5% incidence of HT associated with PTC. PTC represents 70-80% of all cases of thyroid cancer. An interesting result of the study was that when HT presented with PTC the mortality rate was a mere 0.9% compared to 5% for PTC occurrence without HT (Ahn et al. 1230). A theory for this is that there are already cytotoxic T-cells present due to the HT that play in part in hindering the tumor. Still, thyroid cancers in general have low mortality rates when compared with others.

Bringing together this research one can conclude that the precipitating factors that initiate an auto-immune response have conserved factors with several other more popularized and mainstream diseases such as Grave's disease and Type I diabetes and by localizing the brunt of pathogenesis to the CD8 receptor makes studying HT *in vivo* considerably more manageable for researchers. The other side of the coin is that these studies also indicate the immune system is

engaging in an all-out attack on the thyroid as is evident from the presence of at least three different types of cytotoxic killer cells in patients with HT.

The severity of the response has also been heavily linked to future cancer formation (McManus 51). This indicates that HT may be more lethal and have more severe implications than once thought. The susceptibility of patients suffering from HT to other more serious autoimmune diseases, such as lupus, is something that physicians will have to take in account before dismissing a patient as cured and healthy. Finally, these factors justify the notion that surgery (thyroidectomy), once deemed too radical, may be not only a safe cure but also have preventative benefits. The trend seems to simplify to the idea that the longer the immune system is attacking its own tissues the more likely complications are to happen, whether they are other diseases or a dangerous cancer. Table 2 shows, however, that over 57% of cases that sought surgery due to a risk of malignancy only 13% of cases actually became malignant with time so it must be assessed on a case to case basis.

| | Cases (%) | Controls (%) | <i>P</i> value |
|--------------------|-----------|--------------|----------------|
| Proven malignancy | 13 (11.6) | 124 (6.1) | 0.03 |
| Risk of malignancy | 57 (50.9) | 735 (36.0) | 0.002 |
| Pressure symptoms | 38 (33.9) | 852 (41.8) | 0.12 |
| Thyrotoxicosis | 3 (2.7) | 250 (12.3) | 0.004 |
| Patient request | 0 (0.0) | 46 (2.3) | 0.20 |
| Other | 4 (3.6) | 174 (8.5) | 0.09 |

Risk of malignancy – based on a combination of cytology, sonography and clinical suspicion. Some patients had more than one indication for surgery.

Table 2: Indications for surgery: shows the percent of cases that pursued surgery for various symptoms and risks. (McManus et al. 51)

Case Presentation: Differential Diagnosis, Underlying Symptoms

The patient is a 36 year-old female with two children complaining of weight gain, mood swings, joint pain, and fatigue. These are relatively vague symptoms and the reasons for them could range from being benign or idiopathic, to a mood disorder, or a very serious disease. The physician talked with the patient and likely ruled out seasonal or social causes like job stress, or the flu virus because the persistence of symptoms. The physical did not reveal anything of importance, and the patient seemed relatively healthy. Some possible diagnoses at this point are Rheumatoid arthritis, CFIDS (chronic fatigue), Lyme disease, anemia, or cancer. The physician's next step was a battery of laboratory tests. Some of the labs taken were RBC, TSH, ANA, HDL/LDL, and HbA1c. The red blood cell count (RBC) will tell if the patient is anemic, which would explain the fatigue. The cholesterol count is standard and will tell if the patient is at risk of coronary disease, due to diet, or some secondary effect from another disorder. The ANA (anti-nuclear antibody) will test for auto-immune disease. The ANA checks to see if the patient has antibodies to certain antigens identified to be involved in autoimmune response. In an autoimmune disease these antibodies are attacking and killing cells which can cause the destruction of tissues or entire organs.

The labs return with slightly high cholesterol levels, a positive ANA, and high TSH levels. A positive ANA covers a very broad range of autoimmune diseases, like systemic lupus erythematosus or rheumatoid arthritis. Arthritis is very plausible with the joint pain present, but fails to explain other symptoms. Lupus is known to affect any part of the body and cause all of the patient's symptoms. At this point lupus would be included as a differential diagnosis. It is interesting to note that up to 50% of people with lupus develop anemia. Type I diabetes is also an autoimmune condition but since the HbA1c returned as normal, it can be ruled out. The TSH

tests thyroid function, a high TSH count with the symptoms present is very indicative of Hypothyroidism. This is because the hypothalamus is producing a lot of TSH to try to illicit a response from the thyroid, but for whatever reason it isn't working. Thyroid hormones regulate important aspects of metabolism, appetite, and mood. The doctor at this point ran tests for T3 and T4 levels. They turned out to be lower than normal, which confirms the thyroid is not responding to the TSH and not carrying out its normal functions. The elevated cholesterol levels can be potentially explained by a malfunctioning thyroid and a sluggish metabolic rate.

The most common cause of hypothyroidism in the United States is Hashimoto's thyroiditis, so this is naturally a physician's first choice for a diagnosis. Iodide deficiency is another common cause in third world countries but is extremely rare in the US because table salt is iodinated. The symptoms for hypothyroidism include, fatigue, unintentional weight gain, and cold chills. These are consistent with the initial complaints of the patient. Hashimoto's is ten times more likely to show up in women, and this patient at 36 years old, the ideal age to develop the disease. An enlarged thyroid or goiter can be a sign of Hashimoto's but is not always present. The most specific test for Hashimoto's looks for antibodies for several antigens including anti-thyroid peroxidase (anti-TPO), antithyroglobulin (anti-Tg), and to a lesser extent, TSH receptor-blocking antibodies (Ben-Skowronek et al. 339). The patient tested positive for these antibodies, so the diagnosis can be made as Hashimoto's thyroiditis with confidence. One should know that 10-15% of patients with Hashimoto's will test negative for antibodies and some patients with these antibodies will never develop Hashimoto's.

Plan for Care/Treatment Plan

The prognosis for patients with Hashimoto's thyroiditis when diagnosed early is good, with a very low morbidity. The front-line treatment is levothyroxine replacement therapy. Levothyroxine is a synthetic T4 analog. Like T4 it increases the metabolic rate, glycogen breakdown, and gluconeogenesis. It can be taken orally or injected. The usual starting dose is 25-50 mcg/day. The patients TSH levels are monitored every 6-8 weeks by the doctor, and the dosage is changed until optimum TSH levels and thyroid functions are reached. A standard reference range for TSH for adults is between 0.4 and 3.0 microL/mL (Fava, Oliverio, and Guiliano 2009). The medication can take 3-5 days to start becoming effective in treating symptoms. Side effects are rare and include arrhythmias, cramps, diarrhea, nervousness, tachycardia and tremors.

This treatment does nothing to actually protect the thyroid gland from the immune system so the thyroid will eventually be destroyed and may need to be removed surgically. This means replacement therapy is almost always necessary for the rest of the patient's lifespan in order to prevent the onset of symptoms. Due to the need for strict compliance, a physician must make sure that the patient is very educated about their disease and the treatment. Levothyroxine is a generic drug that can be found at under a dollar a pill, so most patients, even those not on insurance should be able to afford it. A physician should make every effort to make sure the patient has access to the drug as it can bring large improvements in quality of life, and will likely increase the patient's lifespan. For patients that are non-compliant the physician can inform them of the risk of myxedema coma which is potentially deadly consequence of chronic hypothyroidism and other complications that are largely avoidable when the medication is taken correctly.

Certain symptoms may persist even with hormone therapy. Some patients continue to alternate between hypothyroidism and hyperthyroidism which makes deciding the right dosage of hormone next to impossible. For others the chronic inflammation of the thyroid can cause compression which can lead to difficulty swallowing or voice problems (McManus et al 51). For these patients a thyroidectomy can be recommended. The patient should know that it is a relatively safe procedure that is almost guaranteed to help their symptoms. It should be made clear that they will still need to take levothyroxine after the surgery and the dosage may even need to be increased due to the thyroid being completely absent from the body.

Those who suffer from one autoimmune disorder are at a significantly higher risk to develop a second autoimmune disease. Hashimoto's has been seen to present along with Multiple Sclerosis, Type I diabetes, and Celiac disease (Wiebolt 790).

Discussion

Compared to others disorders, the pathogenesis of autoimmune disorders are still relatively not well understood. Even if the exact origin of disease is unknown, doctors now have the knowledge and tools to diagnose and treat many auto-immune disorders. Blood tests can reveal the presence of very specific antibodies and synthetic hormones can trick the body into doing what one wants. Autoimmune disease is different from most ailments in that one is fighting one's own body from destroying itself.

Hashimoto's thyroiditis is not relatively well known among the general public, mostly because it is uncommon and is rarely fatal. However, that doesn't mean it can't have huge consequences affecting the quality of life of those who are affected. Many of the symptoms like joint pain and fatigue can debilitate a person, while the mood swings may have detrimental effects on their relationships. The good news is that when properly diagnosed and treated with hormones, a person will most likely be able to live a normal symptom-free life. Hormone therapies such as Levothyroxine are a testament to modern medicine, and only represent the start of the ultimate goal of curing all auto-immune disorders.

What the case study failed to illustrate was that even with all the symptoms described, it is very likely that the Hashimoto's diagnosis would not have been made on the patient's first visit. As noted, the symptoms are vague and can easily be attributed to "not real medical problems". If the patient doesn't have a goiter, similar to the woman in the case study then a physical exam will likely reveal nothing that points towards HT. The key here was extensive blood work, which a physician may be hesitant to do if the patients insurance will not cover it.

Three of the scientific papers cited in this paper were published in 2011, so it is evident that a large amount of research around the world is currently being done on HT. Some of the research

may seem overly specific or narrow but with each new discovery made, the picture becomes more complete. The future of treating HT looks bright as new diagnostic tools and treatments emerge. Though, it's not likely to gain a lot of public attention any time soon researchers know that the key to curing all autoimmune diseases may lie in any one of them, including Hashimoto's thyroiditis.

BS-MD Case Study**Patient name:** Sarah Ricoh**Chief Complaint:**

Patient presents with prolonged fatigue and depression. Also complains of worsening joint pain.

History of Present Illness:

Mrs. Ricoh is a 36 year-old female who says she has noticed drastic and negative changes in her mood and overall health. She notes that she noticed these changes happening about one year ago. She says from that time, she has been experiencing spontaneous mood swings and bouts of depression. She self describes her depression as being highly irritable and losing interest in things she normally enjoys. She says that the symptoms come and go, but are never entirely alleviated. The mood changes also present with fatigue so that she often can't get of bed.

She complains that she has joint pain in her elbows and wrists. The pain developed relatively recently and has been increasing over the last few weeks. She says ibuprofen helps the pain slightly.

She claims that she has no social issues that are severe enough to precipitate these psychological problems. She is married with two children. She says the marriage is healthy, and that her children have no major behavioral problems. She notes that possibly as result of her depression, she has gained 20 pounds and is unable to lose the weight.

Past medical history/Hospitalizations:

2 children-healthy births

Surgeries: none**Allergies:** No known drug allergies**Medications:**

- Ibuprofen for joint pain
- Multi-vitamin daily

Family History:

- Father died at 67 from CHF
- Mother is 64 in good health (menopause at 47)
- Has sister in good health

Social History:

- She has been married for 10 years,
- She has two boys, aged 7 and 9
- Denies substance abuse
- Non-smoker
- Drinks occasionally
- Denies travelling
- Works at a bank

Review of Systems:

General: occasional headaches, denies nausea vomiting, fainting, fever

HEENT

- Head – denies jaw pain, dizziness, syncope
- Ears –denies hearing loss, tinnitus, pain, and vertigo
- Eyes – denies dry, burning eyes; denies problems or changes in his vision, denies blurred vision
- Nose – denies nasal or sinus congestion and epistaxis
- Throat – denies dysphagia, sore throat, and mucosal redness

- Cardiovascular –denies edema, denies arrhythmia and chest pain
- Neck – denies lymphadenopathy, pain, or redness of the lymph glands.
- Pulmonary – denies dyspnea, cough, or respiratory problems such as asthma, bronchitis, wheezing
- Gastrointestinal- denies decreased appetite, heartburn, regurgitation, frequent belching, yellow jaundice, diarrhea, constipation, gas, blood in the stools, black tarry stools or hemorrhoids.
- Genitourinary – reports irregular and heavy menstrual cycles, denies dysuria and hematuria; denies increased frequency or urgency of urination and general complaints
- Neurologic –admits to some paresthesias, denies muscle weakness, syncope
- Musculoskeletal - refer to HPI, denies sensory loss, muscle wasting
- Hematopoietic – denies easy bleeding or bruising
- Psychosocial – refer to HPI
- Skin and breasts- denies easy bruising, skin redness, skin rash, hives, sensitivity to sun exposure, tightness, nodules or bumps, hair loss, breast lump, breast pain.

Physical Examination:

Vitals:

Height- 5'5 Weight-170 lbs HR- 71 RR: 14 BP- 120/80 Temp- 97.5 Pulse ox- 97%

General:

Patient is overweight (BMI 28) and appears to be in mild distress

HEENT:

- Head: normocephalic
- Eyes: PERRL, EOMI. Fundi normal, vision is grossly intact

- Ears: External auditory canals and tympanic membranes clear, hearing grossly intact.
- Nose: No nasal discharge.
- Throat: Oral cavity and pharynx normal. No inflammation, swelling, exudate, or lesions, teeth and gingiva in good general condition.
- Neck: Neck supple, non-tender without lymphadenopathy
- Heart: Normal S1 and S2. No S3, S4 or murmurs. Rhythm is regular. There is no peripheral edema, cyanosis or pallor. Extremities are warm and well perfused. Capillary refill is less than 2 seconds. No carotid bruits.
- Breasts: No masses, tenderness, asymmetry, nipple discharge or axillary lymphadenopathy.
- Genitourinary: deferred
- Musculoskeletal: Indicates joint pain in elbows and wrist (radio-carpal) joint, normal muscular development, normal gait.
- Integumentary : Skin is noticeably dry and cracked, coarse hair, no lesions or eruptions
- Lymphatic: Non-tender, no palpable masses
- Neurological: CN II-XII intact. ANOx3. Strength and sensation symmetric and intact throughout. Reflexes 2+ throughout. Cerebellar testing normal.

Problem list: Fatigue, depression, joint pain

Differential: Lupus erythematosus, rheumatoid arthritis, thyroiditis, CFIDS (chronic fatigue), Lyme disease, anemia, major depressive disorder

Laboratory Data:

Complete blood count:

WBC count: 7.4 k/ml;
RBC count: 6.8 m/ml;
Hemoglobin: 13.7 g/dL;
Hematocrit: 40.6%;
MCH: 31.9 µg;
MCHC: 31.2%;
MCV: 84 fL;
Platelet count: 375,000/cmm;
Total lymphocytes: 6.3%;
Neutrophils: 56%;
Eosinophils: 0.8%;
Basophils: 0.4%;
Monocytes: 4.9%

Thyroid function:

TSH: 9 mIU/L

T3: 75 ng/dl

T4: 3.8 mcg/dl

Lipid panel:

Total cholesterol: 234 ng/dl

Triglycerides : 150ng/dl

HDL: 42 ng/dl

LDL: 115 ng/dl

ANA: Positive

Antithyroglobulin antibody: Positive

Discussion of Case Study

The patient, a 36 year-old female, presented complaining of depression and fatigue. She also noted worsening joint pain. She says the mood changes began spontaneously about one year ago. Upon questioning, she insisted that nothing in her social life could be causing the symptoms. She has also gained 20 pounds in a relatively short amount of time. During the interview she noted that her menstrual cycles had been irregular and heavy. A physical exam produced no significant results other than dry skin.

Major depression is an obvious diagnosis but the fact that it presents with fatigue and joint pain is indicative of several other diseases. Lab tests were done before any anti-depressant treatment was considered. An early onset of menopause could explain the joint pain and mood swings but her mother did not go through menopause until age 47 and she claims her cycles had been getting heavier instead of diminishing.

Fatigue is a generalized symptom, but its prolonged presence could suggest anemia. A CBC was run to obtain a RBC and look for signs of possible infection. All values came back normal. Since her father died of heart failure and because she is currently overweight, a lipid panel was taken to assess her cholesterol levels and risk levels for atherosclerosis and eventual CHF. The results showed she had elevated total cholesterol and LDL.

The joint pain with fatigue shares symptoms with auto-immune disorders such as lupus erythematosus and rheumatoid arthritis. An ANA was ordered to test for the presence of anti-nuclear antibodies, which are antibodies that specifically target the body's own tissues. The ANA returned positive indicating that the patient may be suffering from Lupus or a number of other autoimmune diseases. However, ANA's can sometimes be active in patients with no disease.

Her symptoms included changes in mood and metabolism which in women is often a result of a malfunctioning thyroid. TSH levels along with T3 and T4 were tested. The result indicated high TSH levels and low T3 and T4 levels. This showed the patient was in a state of hypothyroidism. High levels of TSH are being released by the anterior pituitary gland but aren't eliciting a response from the thyroid resulting in low T3 and T4 levels (Kumar 1218).

The hypothyroidism and the positive ANA heavily suggest that Mrs. Ricoh is suffering from Hashimoto's Thyroiditis. An antithyroglobulin antibody test was run to confirm this diagnosis. A positive test very nearly confirms the diagnosis as Hashimoto's.

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