The train of autoimmunity

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Contents

Summary

Autoimmune diseases are a major health problem worldwide. In autoimmune disease the tolerance of the immune system against self-determinants is lost and the immune system causes damage to certain tissues or organs. Disease is often only recognized when advanced damage to tissues has occurred. Treatment of autoimmune diseases is based on anti-inflammatory and immunosuppressive drugs and there is a need to recognize and intervene early in the onset of disease.

The focus of this paper is (subclinical) Hashimoto thyroiditis. The most important implication of subclinical hypothyroidism is high likelihood of progression to clinical hypothyroidism. Subclinical Hashimoto's (Incidence 4-6% in the general population) are facing serious and nonspecific health issues over a period of 7-10 years. They are at risk to develop coronary heart disease, psychiatric disorders, other autoimmune diseases and they experience pregnancy problems.

In daily practice, health complaints can precede formal diagnosis: dysregulated thyroid hormone balance and the presence of anti-TPO and anti-TG auto antibodies in the circulation. This often leads to a 'wait and see' approach, with as a consequence returning visits to the medical professionals without further support to the patient.
Early detection of subclinical Hashimoto's disease will be more successful when protocols are changed: concerning classification and treatment. Anti-thyroid autoantibodies measurement (against Thyroglobulin and Thyroid peroxidase) may be proper for patients with high-normal TSH to distinguish subclinical cases who are at risk of developing hypothyroidism. Though, in reality, anti-thyroid autoantibodies are not measured when the TSH values are in the normal range and there is still a discussion about the normal range, the upper limit of reference range of TSH.

Immune dysfunction may precede the onset of psychiatric disorders and go hand in hand with the development of Hashimoto's disease. Moreover, without optimal thyroid function (even very small fluctuations make a difference), mood disturbance, cognitive impairment and other psychiatric symptoms can occur. Thereby, treatments as usual are not the best choice for people with an autoimmune cause of their psychiatric complaints. Thyroid abnormalities are associated with a poorer response to standard treatments for mood disorders. Subjects with lower thyroid function, even within the normal range, have a poorer response to initial treatment with hormonal replacement therapy.

Diagnosing on time subclinical cases with slight hypothyroidism and properly treating them is essential in order to slow down the progression of the disease and in order to manage the risk of coronary heart disease, psychiatric disorders, and pregnancy problems.

Do you recognize these challenges? What if there is way to help subclinical Hashimoto's?

Introduction

For a century, humankind has been working on getting a clear understanding of the cause of autoimmune diseases and finding a treatment for them. Unfortunately no unambiguously answers have been found yet. Meanwhile the number of people suffering from autoimmune diseases are increasing.

If we want to get better results, we should start doing things differently.

This paper highlights the current challenges and offers an up-to-date multidisciplinary scientific review focusing on one autoimmune disease: Hashimoto thyroiditis. It offers strong rationale on why we should focus on subclinical cases and what the price will be if we don't.

After reading this paper, you will have an up-to-date and multidisciplinary knowledge concerning Hashimoto thyroiditis, and you will know better how to identify subclinical cases and you will have a solution to offer to the subclinical Hashimoto patients which is a surplus to the already used medical protocols.

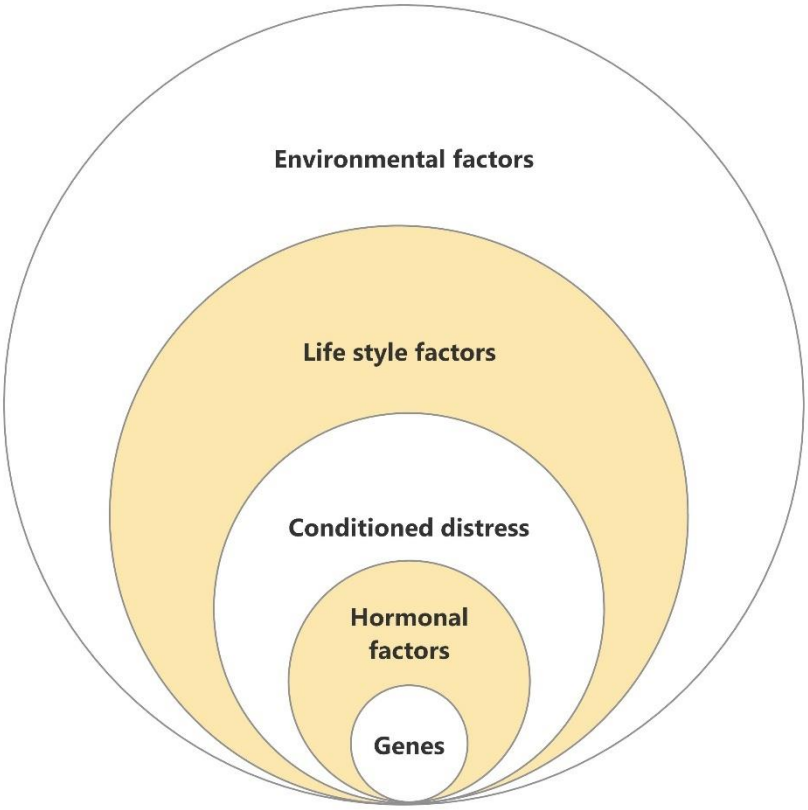
Autoimmune diseases

The idea about the existence of autoimmune disease emerged a century ago [1]. Since then, over 100 autoimmune diseases have been defined. Autoimmune disease is characterized by an aberrant activation of the adaptive immune response with T and B lymphocytes responding to self-antigen [2].
No epidemiologic data are available for many of the autoimmune diseases. This makes it difficult to estimate precisely the prevalence and cost for all autoimmune diseases [3]. Though, studies show undoubtedly that autoimmune diseases cause significant and chronic morbidity and disability [4, 5]. In addition, over the last decades epidemiologists observed a steady rise in autoimmune disease throughout Western world [6, 7], with a compound annual growth rate increase in incidence of 5.57% [8].

Causes

Genetic factors play an important role in the etiology of autoimmune diseases. However, many of the latest research findings as well as the fast growing pace of the increase of autoimmune diseases, point out that it is unlikely that most of the rise can be assigned to an accumulation of genetic predispositions. This is indicating that environmental factors such as

infections, vaccines, dietary components, toxic chemicals are important drivers of the growth of autoimmune diseases [9-11].
In addition to genetic and environmental factors, physiological factors such as hormonal and lifestyle factors may play a role in the development of autoimmune diseases. Thus, the etiology of autoimmune diseases may be multifactorial. The onset of at least 50% of autoimmune disorders is attributed to ‘unknown trigger factors’ [12].



Treatment

A century after the discovery of autoimmune diseases, there is still no cure for them. More knowledge is needed into the etiology and mechanisms of action for these diseases as well as the development of earlier interventions [9, 13]. The world autoimmunity expert, Dr. Noel Rose, makes use of the metaphor of the train of autoimmunity. He emphasises that if we want to be able to help find a way to treat autoimmune diseases, it is essential to step on the train at the beginning before the disease fully manifests itself.

In this paper, the focus is on the autoimmune disease Hashimoto’s thyroiditis. While reading, you may see a resemblance and option for application of the provided information to other

autoimmune diseases. This is greatly due to the fact that: 1) all autoimmune diseases have a great deal in common; 2) it is those common traits that are the most fundamental; 3) autoimmune diseases tend to cluster. When having one autoimmune disease, patients are prone to get a second or a third one.

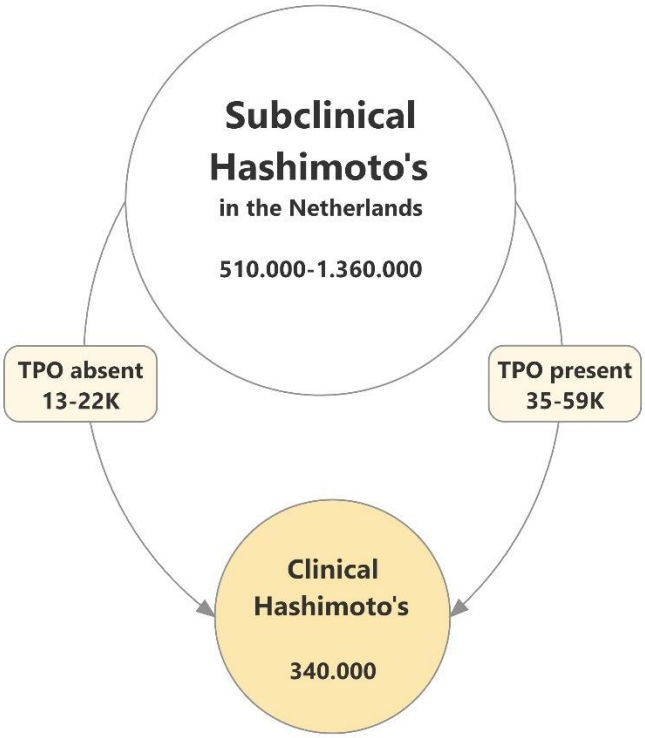
Hashimoto thyroiditis

Autoimmune diseases are broadly categorized in two groups: organ-specific and systemic. Hashimoto's thyroiditis (HT) was firstly discovered in 1912 by Hakaru Hashimoto. Yet, its autoimmune aspect has been demonstrated later in the 1950s. Hashimoto's thyroiditis is an organ-specific autoimmune disorder, which is the most frequent cause of hypothyroidism and goiter. It is a chronic autoimmune inflammation of the thyroid gland. The diagnosis is suspected based on the detection of raised levels of circulating autoantibodies against thyroid peroxidase and thyroglobulin [14]. About 2 % of the general population is suffering from Hashimoto thyroiditis while 80 % of those are women, most often in one of the vulnerable periods: adolescence, pregnancy or pre-menopause. In the Netherlands, around 340 000 people suffer from Hashimoto thyroiditis.

Subclinical Hashimoto thyroiditis

The most important implication of subclinical hypothyroidism is high likelihood of progression to clinical hypothyroidism [15]. Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the patients without diagnosed thyroid disease [16, 17]. Subclinical patients are much more prone to coronary heart disease [29], psychiatric disorders [18], and pregnancy problems [19, 20]. The most common cause of elevated TSH is autoimmune thyroid disease and destruction of functional thyroid tissue. From those with subclinical hypothyroidism, 2-5 % per year will progress to overt hypothyroidism, defined as TSH >20 mIU/L or free T4 below the normal range [21, 22].

Subclinical Hashimoto thyroiditis patients have raised TSH level and normal level of serum thyroid hormones (T4). In most of the cases, increased autoantibodies are also present. Patients with subclinical hypothyroidism have a high rate of progression to clinically overt hypothyroidism: 2.6% each year if thyroid peroxidase (TPO) antibodies are absent and 4.3% if they are present [23].



Thus, anti-TPO measurement may be proper for patients with high-normal TSH to distinguish those at risk of developing hypothyroidism [24].
A well-timed diagnosis of subclinical cases with slight hypothyroidism and a proper treatment is essential in order to slow down the progression of the disease and in order to manage the risk of additional pathology such as coronary heart disease, psychiatric disorders, and pregnancy problems.
In terms of early pharmacological treatment, there is insufficient scientific support of the benefit for levothyroxine therapy in patients with subclinical hypothyroidism, in particular for the group with TSH less than 10 mIU/L [21]. Currently no additional (pharmacological) treatments are available in this phase of the disease.

Challenges

What makes it difficult to detect Hashimoto thyroiditis at early stage?

Subclinical Hashimoto thyroiditis is difficult to diagnose on time due to nonspecific symptoms at an early stage. Since autoantibodies are markers of disease activity, autoantibodies are often able to predict disease. This approach is especially promising for diseases with a long subclinical period, which can take as long as 10 years, a feature of many organ-specific autoimmune diseases, as Hashimoto thyroiditis [25, 26].

Though in practice, antibodies are not measured when the TSH values are in the normal range.

What is the normal upper limit of reference range of TSH?

There is still a discussion in the medical field about the normal range, upper limit of reference range of TSH [27]. Furthermore, there are differences between countries and even internal there are variances of what each laboratory is using as a normal range.
But how to identify subclinical cases if there is still debate about what the reference range of the normal TSH concentrations should be?
A recent study shows that a significant increase in the prevalence of Hashimoto thyroiditis occurred among individuals with a TSH ranging between 2.6–2.9 mU/L and suggests this cut-off value of normal upper limit of TSH [28].

Common autoimmune disorders tend to coexist in the same subjects and cluster in families.

In some cases, autoimmune diseases tend to co-develop in individuals. Hashimoto's disease shows a noticeably higher clustering particularly with adrenal and B-cell autoimmunity [29]. An association of Hashimoto's thyroiditis with both organ specific and non-organ-specific autoimmune diseases has been observed: Addison's disease [30], Type 1 diabetes mellitus [31], pernicious anemia [32], celiac disease [33], multiple sclerosis in females [34], rheumatoid arthritis [35], and vitiligo [36].
It is a fact that Hashimoto's thyroiditis occurs in association with many other autoimmune disorders [36] and corresponding autoantibodies may be helpful in diagnosing these associated diseases. For patients at first presentation of autoimmune thyroid disease and/or displaying nonspecific symptoms, it is recommended to screen for other autoimmune diseases [36].

Psychiatric symptoms as a sign of autoimmunity storm?

Changes in immune activity can cause psychiatric disorders or can effect such disorders [37]. The fact that some psychiatric disorders have an autoimmunity origin is because the brain can be affected by various autoimmune processes and mediators. Immune dysfunction may precede the onset of psychiatric disorders and go hand in hand with the development of

multiaxial comorbidity, including suicidal behavior, metabolic, and autoimmune disorders [38]. Moreover, without optimal thyroid function (even very small fluctuations make a difference), mood disturbance, cognitive impairment and other psychiatric symptoms can occur [39, 40].

Affective disorders: depression, anxiety and bipolar disorder

Affective disorders often are associated with thyroid dysregulations [41, 42]. Furthermore, thyroid autoantibodies have been frequently assumed to play a role in some affective disorders [39]. *Depressive disorders* in patients with thyroiditis is independent of the thyroid function and indicates that not only mood but also *anxiety disorders* may be associated with Hashimoto disease [18, 43-45]. Evaluations in the postpartum target depression show an association with thyroid autoantibodies and not with thyroid function [46]. Thus, the autoimmunity plays an independent role in these complaints.
Furthermore, increasing evidence suggests that inflammation and immune dysregulation play an important role in the pathogenesis of *bipolar disorder* [47, 48]**.** Thyroid autoimmunity has been suggested to be an independent risk factor for bipolar disorder [49, 50]. Such thyroid abnormalities are seen as modulating bipolar disorder manifestation with implications on the its severity, prognosis, and outcome [51].

Non-affective disorders

Anti-thyroid autoantibodies are present in 9% of psychiatric patients with nonaffective disorders [52]. Thus, this association may not be specific for affective disorders per se. Some examples are: 1) the estimated significant relationship between fluctuations in anti-thyroid autoantibodies and psychotic and mood symptoms in people with *borderline personality disorder* [53]; 2) immune dysregulation is suggested to play an important etiological role also in *schizophrenia* and potentially driving neurodevelopmental pathways [54].

Treatments as usual are not the best choice

Current standard treatments may not be the best choice for people with psychiatric complaints with an autoimmune cause. Thyroid abnormalities are associated with a poorer response to standard treatments for mood disorders [55]. Subjects with lower thyroid function, even within the normal range, have a poorer response to initial treatment [55].

Drugs that treat depression by manipulating the neurotransmitter serotonin in the brain may also affect a patient's immune system [56]. This is caused by serotonin that is exchanged between key cells in the immune system and the fact that serotonin facilitates the activation of an immune response. Selective serotonin reuptake inhibitors drugs may restore a healthy immune function in people who are depressed and prone to infections. Though, the new research findings warn that they might also bolster immunity to such extent that an autoimmune disease is triggered [57, 58].
Lithium therapy is often used as treatment of bipolar disorder. Lithium administration is known to be associated with the development of thyroid dysfunction [59] as well as it also exerts an effect on the immune system [60]. By patients with initially high anti-thyroid antibodies, lithium leads to significantly fluctuating titres [61, 62].

Wait and see approach of subclinical cases

As already discussed, patients with subclinical hypothyroidism have a high rate of progression to clinically overt hypothyroidism. And if the subclinical Hashimoto's are not classified and treated for some other condition, most often due to lack of clear disease profile or lack of available evidence-based help for subclinical Hashimoto's, for a long period of time the wait and see approach takes place.
Have you ever considered that stress reactivity might be a missing link?

A missing link: Conditioned stress reactivity response

Physical and psychological distress play a role in the development of autoimmune disease as Hashimoto's thyroiditis [63]. Many studies confirm the effect of different stressors on the function of the immune system [9, 10]. In addition, many retrospective studies have shown that up to 80% of patients reported uncommon emotional stress before disease onset [64]. In addition to the fact that distress causes disease, the disease itself causes considerable distress in the patients, creating a vicious cycle.
The immune system plays a role in sensing external threats. But what happens when it has been programmed to stay in constant alert? And what are the factors that influence this programming?

A biological embedding model postulates that childhood stress gets 'programmed' into macrophages through epigenetic markings, posttranslational modifications, and tissue remodelling [65]. Distress is not just a cause of dramatic events. Distress ranges from emotional, behavioural, interpersonal, school and stress-related adjustment problems, to

more severe difficulties such as mental health problems, misbehaviour and criminal offending [66]. As a result of distress, cells are prone to excessive inflammatory signalling via exaggerated cytokine responses to challenges and decreased sensitivity to inhibitory hormonal signals. In addition to the other exposures and genetic predispositions, the inflammation causes pathogenic mechanisms which lead to chronic disease.
This excessive inflammation tendency may be further increased via certain behavioural and hormonal responses. Childhood distress leads to the increase of the risk of substance abuse [67], obesity [68], mental conditions [69], sexually transmitted diseases [70], suicide attempts [71], and physical diseases as ischemic heart disease [72], autoimmune disorder later in life and shortening of the life span [73]. Though, early adverse experiences show to have detrimental effect on health independently of certain behaviours [74].

Observations about the effect of stress on the onset and course of autoimmune disorders show that the psychoneuroimmunology interactions are bi-directional [11]. There is evidence that brain-to-immune interactions are highly modulated by psychological factors which influence immunity and autoimmune disease [75]. Early adverse circumstances are shaping the developmental trajectories, particularly in the areas of stress reactivity and physical or mental health [76, 77].

Brain changes

Early childhood is an extremely delicate period in human development. During this period the brain, specifically the circuitry governing emotion, attention, self-control and stress, is formed by the interplay of the child's genes and experiences [78]. Childhood ill-treatment modifies the relationship of depression with hippocampal volume [79]. Childhood ill-treatment (emotional neglect, psychological, physical, sexual abuse) decreases hippocampal volume which is related to major depressive disorder.
The childhood adversities, even subtle forms of childhood stress (e.g. having a depressive parent) leads to changes in the brain in size and volume, altering the expression of the genes that control a stress hormone output, triggering an overactive inflammatory stress response and predisposing to adult disease [80]. Early life stress can induce multiple changes across the brain-gut axis that contribute to the susceptibility to develop stress-related disorders [81]. How the gut functions: digestion of food, presence of food sensitivities and/or allergies, and processing of stress may be a sign of earlier difficult life experiences. Recent study reports that people with altered microbiomes have differently shaped brains. The hypothesis is that it is probable that this relationship isn't unidirectional. The scientists

state that the signals the gut and its microbes get from the brain of someone with an early adverse event history may lead to lifelong changes in the gut microbiome [81].

Hormonal changes

The environment in which a person grows up has a considerable impact on the development of hormonal responses to stress [82]. Any imbalance to an organism's homeostasis produces a complex stress response that involves the coordinated activation of neuroendocrine and autonomic systems. The hypothalamic–pituitary–adrenal (HPA) axis is important. It is triggered by stressors of various sources (physical, emotional, immunological, etc.) to provoke the systemic release of glucocorticoids [83].
HPA axis's development and maturation, also called the stress axis, is influenced by the safe environment people encounter as kids [37]. Adverse early experience has an continuous impact on the responses to stress, which is marked by an abnormal metabolism of thyroid hormones, which reprogams how the axis responds to stress later in life [10]. Early life trauma is associated with decreased peripheral levels of thyroid-hormone T3 in adolescents [84]. The quality of maternal care is associated with changes in the relationship between the precursor thyroid-hormone T4 and the more active T3. Good maternal care is associated with increased conversion of T4 to T3.
It is presumed that the stress-triggered neuroendocrine hormones lead to immune dysregulation, which ultimately results in autoimmune disease, by altering or amplifying cytokine production [85].

What if there is a way to help?

Stress is inevitable part of life and not bad per se [86]. When under stress, healthy individuals quickly respond, come back to the baseline and recover [87]. Stress can influence the immune system, either by stopping it responding to stress or by bringing an overstimulation and an exaggerated reaction, as it generally occurs with autoimmune diseases as Hashimoto's, where the stress response is not shut off [88].
While there is an agreement between medical professionals and patients that stress plays a role not only in the onset of many disease processes, but also in its exacerbation, there is no clinical research on particular protocols which may be helpful for subclinical autoimmune diseases such as subclinical Hashimoto's thyroiditis.
Different stress reactions should be discussed with autoimmune patients. In addition to the common triggers (e.g. infection, trauma), patients should be asked about psychological stress [8]. Furthermore, recent studies highlight the importance of taking personality features

and individual coping strategies into account when evaluating patients with Hashimoto thyroiditis [89]. By susceptible subclinical Hashimoto's thyroiditis patients, the treatment should include a psychoneuroimmunological approach and an intervention of reprogramming the stress-related immune imbalance. Furthermore, the exploration of interrelationship between stress and disease may lead to the identification of novel anti-inflammatory agents with clinical potential for use in treatment of autoimmune inflammatory diseases [90].
For patients with childhood adversities, the usual stress reduction techniques may not work. This is due to the fact that the secure attachment has been conditioned to the threat response. It is essential to spend time working with the multiple mind and strengthen the patient ego before starting with reprograming the body stress response.
Emotions are changes in both body and brain states in response to different stimuli [91]. Physiological changes (e.g., muscle tone, heart rate, endocrine release, posture, facial expression, etc.) occur in the body and are relayed to the brain where they are transformed into an emotion. Over time, emotions and their corresponding bodily changes become associated with particular situations and their past outcomes. An emotional response is basically the antibody that reacts to an invading stimulus, that is selected by that stimulus. Thus, consciousness and emotions as states of the body, in particular, the immune system.

With this in mind, the 'Reset your immune system' eHealth series has been developed. This series addresses the role of personality on the body's autoimmune reaction. A personality has three components: emotion, cognition, and behaviour, three training programs relate respectively to 'Hashimoto's heart', 'Hashimoto's head', and 'Hashimoto's gut'. 'Hashimoto's heart' guided online training is available for clinical testing for subclinical Hashimoto's with psychological symptoms and clinical Hashimoto's.

Conclusions & questions

Autoimmunity (AI)

- Autoimmune diseases represent a major and fast growing health problem
- Autoimmunity issues are often recognized late, when the damage is done
- We need to put emphasis on studying triggers, causes and cure
- Autoimmune diseases should be approached also as a family

Hashimoto thyroiditis (HT)

- HT is an interesting and relevant member of the AI family

- We need to recognize and intervene HT early in the onset of disease (‘step on the train early’)
- Subclinical HT/hypothyroidism knows a high likelihood of progression
- Subclinical Hashimoto’s are facing serious and nonspecific health issues
- No (pharmacological) treatments are available in the subclincial phase of the disease
- A long period of ‘wait and see’ leads to high costs for patient, society and health care system
- Early detection requires changes in cut off values and testing procedures
- If there is an indication for one autoimmune disease, the patient should be screened for others

Psychoneuroimmunology (PNI)

- Immune dysfunction often precedes the onset of psychiatric disorders or can effect such disorders
- Current standard treatments might not be helpful, or even can trigger an autoimmune storm
- Conditioned distress effects the onset and course of autoimmune disorders like HT
- This complex bi-directional relation should become integral part of treatment
- Autoimmune patients need to learn how to shut off stress responses
- Both subclinical and clinical cases can be trained. However, an early intervention increases the health benefits
- The PNI approach is focused on the reprogramming the stress-related immune imbalance

Discussion

Which of the conclusions of this white paper do you recognize from your daily practice?
Are you open for discussion? What insights would you like to bring to the table?
Are you interested to participate in the scientifically validation of this innovative protocol, in order to improve the life of your (Subclinical) Hashimoto’s patients?

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