The Amsterdam autoimmune thyroid disease cohort
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Summary
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Aim of this thesis

Autoimmune thyroid disease (AITD) encompassing Graves’ hyperthyroidism and Hashimoto hypothyroidism, is a common disorder especially in women, and both genetic and environmental factors are involved in its pathogenesis. The main aim of this thesis was to investigate whether or not it is possible to delineate familial, environmental and immunological risk factors for AITD in order to predict the development of AITD.
To this end a prospective study was carried out in 803 healthy female relatives of patients with documented proof of AITD, known as the Amsterdam AITD Cohort.
The data of this study provide new insights in the prevalence, incidence and risk factors of AITD. Knowing the family history of AITD combined with the found immunological and environmental risk factors we constructed a prediction model for the development of overt hypo- or hyperthyroidism in female relatives of patients with proven AITD.

Summary of the results

In chapter 2 we present a review of known environmental factors involved in the pathogenesis of AITD.

In chapter 3 we report on baseline characteristics of the Amsterdam AITD Cohort.
The females with thyroid dysfunction were older than the euthyroid subjects and age appeared to be an independent risk factor for hypothyroidism. Estrogen use was associated with a lower risk, and pregnancy with a higher risk for having hyperthyroidism.
The prevalence of autoimmune thyroid dysfunction in our Amsterdam AITD cohort was higher than in the general female population, thereby demonstrating that first- or second-degree female relatives of patients with proven AITD are indeed at higher risk for AITD.
The observed prevalence of TPO antibodies in our cohort (24%) fits in nicely between that in the general female population (ca. 10%) and that found in first-degree relatives of AITD patients (ca. 45%). In the euthyroid subjects a dose-dependent relationship was found between serum TSH and TPO antibody level.
Smoking and estrogen use were negatively correlated with the presence of TPO antibodies.
The high prevalence of AITD at baseline supports the importance of particular factors in its pathogenesis. To a certain extent interaction between familial background and environmental factors may determine whether Graves’ or Hashimoto’s disease will develop.

In chapter 4 we investigate the possible relationship between AITD and infection with Yersinia Enterocolitica (YE). YE might play a role in the development of AITD, whilst infection with YE produces a lipoprotein that can cross-react with the TSH receptor. Clinical evidence in support of this hypothesis has been inconclusive. We determined IgG and IgA antibodies to virulence-associated outer membrane proteins (YOPs) of YE. At study entrance the prevalence of YE infection was higher in AITD relatives than in controls. However the prevalence of YOP Ab did not differ between AITD relatives with a normal or abnormal TSH. Also the prevalence of TPO-Ab in the euthyroid AITD relatives was not different between YOP Ab positive and negative subjects. In conclusion, healthy female relatives of AITD patients have an increased prevalence of YOP antibodies, but this phenomenon is not related to the presence of TPO antibodies or abnormal thyroid function. Susceptibility genes for AITD may also confer a risk for YE infection.

In chapter 5 we looked for evidence of involvement of environmental stress exposure on AITD. Recently Experienced Stressful Life Events, Daily Hassles, and mood (tendency to report positive and negative affects) were assessed in 759 euthyroid subjects and related to TPO antibody status as early marker of AITD. The number and impact of stressful life events, the number and impact of daily hassles, and the scores on the affect scales were similar in TPO-Ab positive and TPO-Ab negative subjects. We conclude that the exposure to stress is not related to the presence of TPO antibodies in euthyroid women.

In chapter 6 we searched for markers on peripheral blood lymphocytes in early stages of AITD. Our aim was to test the hypothesis that activation of CD4+ T cells is such a marker in healthy relatives of AITD patients. We performed a controlled study on 20 TPO-Ab positive and 20 TPO-Ab negative euthyroid female relatives in whom we studied the percentages of circulating subsets of activated (MHC class-II, CD25 (IL-2R), CD71 or CD69+) CD4+ T cells and the level of the soluble (s)-IL2R in serum. We found that euthyroid female relatives did not show an activation of their T cell
system, but instead a reduced expression of CD25 on CD4+ T cells. The level of the shed IL2R in serum was also lower in comparison with levels found in healthy control females. A reduced T cell activity was found in both TPO-Ab positive and negative relatives. Interestingly, current smoking seemed to correct for this reduction.

In conclusion, female relatives with at least one 1st or 2nd degree relative with an AITD show signs of a reduced expansion capability of their T cell pool. It is hypothesized that a defect in T regulatory cells promotes thyroid autoimmunity.

In [chapter 7](#) we describe the prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives of patients with AITD using the Thyroid Events Amsterdam (THEA) Score. Family members of patients with AITD are at increased risk for AITD, but not all will develop overt hypothyroidism or hyperthyroidism. Our goal was to develop a simple predictive score that has broad applicability and is easily calculated at presentation for progression to overt hypothyroidism or hyperthyroidism within 5 years.

We conducted a prospective observational cohort study of 790 healthy first- or second-degree female relatives of patients with documented Graves or Hashimoto disease in the Netherlands. Baseline assessment included measurement of serum thyrotropin (TSH), free thyroxin (FT4), and thyroid peroxidase (TPO) antibody levels as well as assay of *Yersinia enterocolitica* antibodies. We also gathered data on family background, smoking habits, use of oestrogen medication, pregnancy, and exposure to high levels of iodine. In the follow-up, thyroid function was investigated annually for 5 years. As main outcome measures, termed *events*, we looked for overt hypothyroidism or overt hyperthyroidism.

The cumulative event rate was 7.5% over 5 years. The mean annual event rate was 1.5%. There were 38 hypothyroid and 13 hyperthyroid events. Independent risk factors for events were baseline TSH and TPO antibodies in a dose-dependent relationship (for TSH the risk already starts to increase at values >2.0 mIU/L) and family background (with the greatest risk attached to subjects having 2 relatives with Hashimoto disease). A numerical score, the Thyroid Events Amsterdam (THEA) score, was designed to predict events by weighting these 3 risk factors proportionately to their relative risks (maximum score, 21): low (0-7), medium (8-10), high (11-15), and very high (16-21). These THEA scores were associated with observed event rates of 2.7%, 14.6%, 27.1%, and 76.9%, respectively.

An accurate simple predictive score was developed to estimate the 5-year risk of overt hypothyroidism or hyperthyroidism in female relatives of patients with AITD. However, in
view of the small number of observed events, independent validation of the THEA score is called for.

In chapter 8 we evaluate prospectively the involvement of environmental factors in the development of overt autoimmune hypothyroidism and hyperthyroidism. Evidence for involvement of environmental stimuli has been obtained mostly by association in retrospective cross-sectional case-control or population-based studies, open to potential (recall) bias. Attempting to avoid potential bias we performed a nested case-control study within the prospective observational Amsterdam AITD cohort-study, in which 790 healthy euthyroid women with at least one 1st or 2nd degree relative with documented AITD were followed for five years. Thyroid function and exposure to environmental stimuli were assessed annually. Contrast in environmental exposure was made between females who developed overt AITD and females who did not (matched for age and duration of follow-up). At baseline, exposure to environmental factors was not different between the 51 cases (38 hypothyroid and 13 hyperthyroid subjects) and their 102 controls. The frequency of Yersinia infection and oral estrogen use remained similar between cases and controls. But at the time of event hypothyroid cases were less often current smokers (p=0.083) and more often in the postpartum period (p=0.006) than their controls, whereas hyperthyroid cases had been pregnant more frequently (p=0.063). Exposure to stress at study entrance, at one year before event and at the time of the event was not different in cases as compared to their respective controls. A rather intriguing and yet still unexplained finding was the elevated affect state of our subjects compared to data from the general female population, reflecting a reactive affect balance style.

The data suggest that cessation of smoking and the postpartum period are related to autoimmune hypothyroidism, whereas autoimmune hyperthyroidism is less frequent in women who have never been pregnant. Stress exposure was not related to either hypo- or hyperthyroidism. The limitation of this prospective observational study is its limited sample size.

Finally, in the general discussion (chapter 9) an overview of the above mentioned studies is presented, and their scientific and clinical implications are discussed.
In short, the results of our studies point to an increased risk for developing AITD in the context of a positive familial background of AITD. The risk to develop overt autoimmune hypo- or hyperthyroidism in the next 5 years can be estimated with the Thyroid Events Amsterdam (THEA) Score. A number of environmental factors (like smoking, estrogen use, and pregnancy) modulate the risk.