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Chapter 1
General Introduction

Background

In 1956 Roitt and Doniach described antibodies against thyroglobulin in serum of patients with Hashimoto disease (1). Also in 1956 Adams and Purves discovered long acting thyroid stimulator (LATS) in serum of patients with Graves’ disease, the first description of thyroid stimulating autoantibodies (2). In the same year Rose and Witebsky generated experimental hypothyroidism in rabbits by immunization with thyroid homogenate (3). A concept of autoimmune thyroid disease (AITD) was born.

Autoimmune thyroid disease especially affects women. The prevalence of AITD is 6 to 8x higher in females than in males. The annual incidence of hyperthyroidism and hypothyroidism in the general adult population is estimated as 1 to 2 and 3 to 4 cases respectively per 1000 women (4). AITD has shown a tendency to cluster within families. Both Graves’ disease and Hashimoto’s disease may occur in the same family (5). Relatives have a higher risk of developing AITD than the general population (6). Twin studies indicate that genetic factors account for about 70% of the risk to develop AITD (7,8). Consequently environmental factors may contribute for about 30%. Although AITD has a very low mortality, it is associated with significant morbidity, both physically and mentally, and leads to diminished quality of life (9). Lifelong treatment is the rule rather than the exception.

In AITD the immune system produces autoantibodies that attack the thyroid gland thereby either stimulating thyroid cells to produce an excess of thyroid hormone or destroying thyroid hormone producing cells, resulting in Graves’ hyperthyroidism (GH) and Hashimoto’s hypothyroidism (HH) respectively. When hyperthyroidism emerges, the patient complains of loss of energy, severe weight loss, palpitations, excessive perspiration, accelerated bowel activity with diarrhoea, goiter, and agitation or nervousitas. Frequently, ophthalmopathy occurs. When hypothyroidism develops, the patient complains of hoarsening of voice, loss of energy, loss of hair, weight gain, dry and thick skin, and intolerance for low temperature.

Either way, if not recognized and properly treated autoimmune thyroid dysfunction results in impaired cognitive function and mood disorders.
Aim of the study

In order to evaluate the interaction between familial background, immunological and environmental factors involved in the etiology of AITD we assembled a cohort of 1\textsuperscript{st} or 2\textsuperscript{nd} degree female relatives of patients with proven AITD.

Firstly, the study was designed to assess environmental and immunological determinants of AITD in this population at risk. Investigated were the pattern of familial occurrence of AITD, environmental factors such as stressful life events and daily hassles in combination with affect state, smoking, pregnancy, estrogen medication, iodine intake, and Yersinia infection. Also associations between thyroid function and immunological factors were investigated such as thyroid stimulating immunoglobulins (TSI), thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab).

The second aim was to investigate the possibility to predict the development of overt AITD within 5 years, in this study population at risk.

We hypothesized that it would be possible to delineate significant environmental and immunological determinants for AITD in this study. Knowing the family history of AITD combined with these immunological and environmental risk factors we hypothesized that we could construct a prediction model for AITD in female relatives of patients with proven AITD.

Study design

Females willingly to participate in our study, were recruited from all over the Netherlands through patients visiting our department, through advertisements in local newspapers, and through thyroid patient self-support associations.

All subjects were seen at our Institution and gave their informed consent. We screened 1003 female subjects with at least one 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative with documented autoimmune hyper- or hypothyroidism, who were in self-proclaimed good health, without a history of thyroid disease, and between 18 and 65 years of age. We checked the medical history of the affected relative(s) regarding the autoimmune nature of their thyroid disease after obtaining their informed consent. Autoimmune thyroid disease for this purpose was defined as documented hyper- or hypothyroidism in the presence of autoantibodies against thyroid peroxidase (TPO), TSH-receptor autoantibodies, histology compatible with autoimmune thyroiditis, or thyroid eye disease.
In 200 of the 1003 screened subjects absolute proof of the autoimmune nature of the thyroid disease in at least one family member was lacking, leaving 803 participants to be included in the presented cohort study. After excluding the 13 females with overt hyper- or hypothyroidism at baseline, 790 first or 2nd degree female relatives of AITD patients were eligible for follow-up. Endpoints of follow-up were the development of overt hyperthyroidism or hypothyroidism (cases) defined by abnormal TSH values in combination with abnormal fT4 or fT3 values in plasma. Endpoints were assessed every year for 5 years.

At each visit blood was sampled for assay of TSH, fT4, TPO-Ab, Tg-Ab, and TSI. Also information was collected on smoking habits, use of oral contraceptives or other estrogens, the number of pregnancies, exposure to iodine excess, Yersinia enterocolitica infection and the amount of stress exposure.

Based on the expectation to assemble a cohort of 1000 females a power calculation had been performed. About 50% of the annual incidence of hyper- or hypothyroidism in adult women is of autoimmune nature. This points to an estimated annual incidence of 0.2% for overt autoimmune thyroid disease (AITD) in women. About ten out of every 1000 women will develop overt AITD within a time span of five years. We assumed an eightfold increase in incidence in female relatives of patients with AITD relative to the general population. When thousand 1st or 2nd degree female relatives of patients with proven AITD are included the expected number of females with newly diagnosed overt AITD after five years of follow-up will be 80. When 160 controls are selected, than the study will have a 80% power to identify risk factors with an odds ratio of at least 2.25, provided that the prevalence of the risk factor in the control group is at least 25%. For risk factors with a lower prevalence (e.g. 10%), a power of 80% will be achieved when the odds ratio is somewhat higher (e.g. 3.0).

Outline of this thesis

In chapter 2 an overview of known environmental factors and their possible pathogenic mechanisms in relation to AITD is described.

In chapter 3 baseline characteristics of the assembled cohort are presented and the observed risk factors for and prevalence of AITD in the cohort are described.

In chapter 4 the hypothesis is that infection with Yersinia Enterocolitica (YE) is more prevalent in the cohort than in control women of the Dutch population. It was also investigated whether YE infection was more prevalent in the euthyroid participants of the cohort with TPO-Ab then in those without TPO-Ab.
In chapter 5 the hypothesis is that exposure to stressful life events results in TPO-Ab production. Stressful life events have been shown to precipitate GH but the evidence was criticized for recall bias. The role of stress in the pathogenesis of HH has not well been studied. A possible association between exposure to stress and the prevalence of TPO Ab is looked into by relating exposure to stress measured by self-reported questionnaires validated for the Dutch situation to the presence of TPO Ab in still euthyroid subjects at study entrance.

In chapter 6 the hypothesis is that T cells in the peripheral blood will have signs of activation in the early stages of thyroid autoimmunity. Cell membrane expression of several relevant molecules are studied in peripheral lymphocytes by measuring the fluorescence of these cells after incubation with marker specific fluorescence; a contrast was made between TPO-Ab positive and negative euthyroid subjects in a random sample of the cohort at study entrance.

In chapter 7 the hypothesis is that familial, immunological and environmental factors precede conversion to overt AITD so that a predictive model can be constructed. We evaluate whether we can predict from baseline characteristics who will develop clinically overt AITD in the next five years. Subsequently a prediction model of progression to overt hypo- or hyperthyroidism in euthyroid female relatives of patients with autoimmune thyroid disease by the THEA (THyroid Events Amsterdam) score is presented.

In chapter 8 the hypothesis is that particular immunological and environmental factors will change in the years preceding the development of overt AITD analysed in a nested case-control study in the 5 years follow-up of the cohort.

In the general discussion (chapter 9), an overview of the above mentioned studies is presented, and their scientific and clinical implications are discussed.
References