PROGRESSION FROM EUTHYROID AUTOIMMUNE DISEASE TO CLINICAL DISEASE: HOW OFTEN, HOW SOON?

Effraimidis G, Strieder TG, Tijssen JG, Wiersinga WM. **Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study.** Eur J Endocrinol 2011;164:107-113. Epub October 18, 2010.

BACKGROUND

The purpose of the study was to evaluate in a prospective manner the progression from euthyroidism to overt autoimmune hypothyroidism or hyperthyroidism and to examine the involvement of certain environmental factors in the development of events.

METHODS

The prospective Amsterdam autoimmune thyroid disease (AITD) cohort consisted of 803 female subjects between 18 and 65 years of age, with no history of thyroid disease, who were in self-proclaimed good health and had at least one first- or second-degree relative with documented AITD. At entry into the study, 13 participants were diagnosed with active disease and excluded, leaving 790 women for follow-up. They were seen every year during a 5-year period.

Subjects received yearly thyroid tests and were asked to fill in questionnaires on smoking habits, pregnancy, estrogen treatment, and iodine excess in the previous year. End points of the study were either completion of the 5-year follow-up or the development of overt hypothyroidism or hyperthyroidism.

Hypothyroidism developed in 38 women (4.8%), 34 with Hashimoto's disease and 4 with postpartum thyroiditis, and hyperthyroidism developed in 13 (1.6%), 11 with Graves' disease, 1 with postpartum thyroiditis, and 1 with silent thyroiditis. For each of these 51 patients, 2 controls were selected from the remaining subjects, matched by age at study entrance, and the analysis of their data was limited to the same visit at which the case patients had reached their end point, thereby controlling for exposure to environmental factors for precisely the same follow-up period.

The average period between study entrance and the occurrence of an event was 3 years. At baseline, the 38 patients with hypothyroidism already had higher thyrotropin (TSH), lower free thyroxine (T_4) and higher thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibody (TgAb) serum concentrations than their 76 age-matched controls, and the difference between the two groups persisted at 1 year before occurrence of the event. At baseline, 7 of the 38 women in whom hypothyroidism developed had subclinical hypothyroidism; excluding these 7 patients did not alter the results.

Clinical

THYROIDOLOGY

In the 13 patients with hyperthyroidism, neither TSH nor free T_4 values differed between patients and controls at baseline or at 1 year before the event, but the prevalence and the titers of antibodies was higher in patients than in controls. At baseline, 2 subjects had subclinical hyperthyroidism, but as in the women with hypothyroidism, excluding these two patients from the analysis did not alter the results.

The difference in TPOAb and TgAb concentrations was not significant between patients with hypothyroidism and those with hyperthyroidism, neither at baseline nor at 1 year before occurrence of the event.

Smoking status was similar in controls and patients at entrance and at 1 year. However, there were fewer current smokers among patients with hypothyroidism than among controls (13% vs. 28%, P = 0.083).

However, there were more cases of postpartum hypothyroidism in the patients than in the controls (8 of 38 [21%] vs. 3 of 76 [4%], P = 0.006). Postpartum hyperthyroidism developed in 2 of 13 (15%) patients versus 1 of 26 (4%) controls (P = 0.06).

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The use of oral estrogens did not differ between patients and control at any time.

CONCLUSIONS

The data suggest that progression toward overt autoimmune hypothyroidism is a gradual process

taking several years, but overt autoimmune hyperthyroidism develops much faster.

The authors confirmed previous studies (1,2) showing the predictive value of mild elevations of serum TSH and the presence of positive thyroid antibodies in the future development of clinical hypothyroidism and suggested that progression toward overt autoimmune hypothyroidism is a gradual process, taking several years. In the Whickham (3) survey , the annual rate of progression from subclinical to overt hypothyroidism was 3% in women with elevated TSH values (> 6mU/L), 2% in women with positive antibodies, and 4.3% in the presence of an elevation of both serum TSH and TPOAb.

Effraimidis et al. studied a selected population of euthyroid women, ages 18 to 65, with a family history of thyroid disease. Within 5 years after the initial examination, 38 of 790 women (4.8%) had overt hypothyroidism; 7 of them already had subclinical hypothyroidism at entrance to the study. We do not know for how long their serum TSH was in the upper limit of normal and for how long they had positive antibodies. Interestingly, the episodes of postpartum thyroiditis were similar in patients and controls at study entrance.

For the 13 women (1.3%) in whom hyperthyroidism developed, the only significant difference between the groups was the higher incidence and higher TPOAb titers in patient versus controls, both at entrance to the study and at 1 year before occurrence of the event. Two of 13 in the hyperthyroid group already had subclinical disease at entrance. The authors did not state the time elapsed for hyperthyroidism developing in the 2 patients with subclinical hyperthyroidism at study entry. At study entry, in the

patients with hypothyroidism, serum TSH and TPOAb concentrations were higher and serum free T_4 levels were lower than in controls.

In contrast, baseline serum TSH and free T_4 concentrations were not different between patients with hyperthyroidism and controls, and this was still true 1 year before the occurrence of the event, suggesting that the transition from euthyroidism to overt autoimmune hyperthyroidism develops quickly, in months rather than years. The authors mentioned their own previous study, in which the duration from Graves' disease symptoms until diagnosis was 4 months.

Several environmental factors were studied in this particular population. Smoking status did not differ between patients and controls at baseline or 1 year before the event. The proportion of current smokers was lower in the patients with hypothyroidism than in controls, but only at the time of the event, although it was of marginal statistical significance (P = 0.08).

Recent reports cited by the authors showed that smoking protects against the development of TPOAb and also against the development of hypothyroidism. No difference was found in the influence of smoking between patients with hyperthyroidism versus controls.

Pregnancy was a factor in both patients with hyperthyroidism and those with hypothyroidism. Postpartum thyroiditis was significantly higher in hypothyroidism than in controls, but was not statistically significant in the patients with hyperthyroidism versus the controls (P = 0.06).

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The strength of the study is its prospective nature, with annual assessments during 5 years of followup in a selected population; the authors stated that they are not aware of studies assessing the transition from euthyroidism to overt autoimmune hypothyroidism or hyperthyroidism in a structured, prospective manner.

The authors proposed a model for the natural history of AITD, arising from the interplay between a particular genetic background involving multiple genes, accounting for 70% of the risk of AITD and a variety of environmental factors, accounting for about 30% of the risk. Smoking and a low iodine intake favor development of hyperthyroidism, whereas not smoking and a high iodine intake favor development of hypothyroidism. The transition from euthyroidism to overt hyperthyroidism occurs in months, provoked, for example, by stress and pregnancy, whereas the transition from euthyroidism

may take several years, triggered by pregnancy (postpartum period) and by quitting smoking.

The dilemma for practicing endocrinologists from this and previous studies on the management of subclinical hypothyroidism is if and when thyroid therapy is indicated, since the vast majority of patients are asymptomatic. The recommendations suggested in the literature are controversial (4), because there are no robust data favoring T_4 therapy, with the exception perhaps of pregnancy or for women planning a pregnancy. If thyroid replacement therapy is not given, how often do these patients need to be tested?

Similar questions arise in the treatment of women with euthyroid chronic thyroiditis. There are no clear answers, but it would depend on several factors, among them age and planning a pregnancy.

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