Low stress level is not causally related to biochemically less severe Graves' disease in older patients

Vos XG, Smit N, Endert E, Brosschot JF, Tijssen JG, Wiersinga WM. Age and stress as determinants of the severity of hyperthyroidism caused by Graves' disease in newly diagnosed patients. Eur J Endocrinol 2009;160:193-9.

SUMMARY

BACKGROUND The pathogenesis of Graves' disease is multifactorial, with genetic and environmental factors playing key roles in the clinical manifestations of the disease, including a relationship between stressful events in the year preceding the diagnosis of Graves' hyperthyroidism. Although environmental stimuli may provoke Graves' hyperthyroidism in genetically susceptible individuals, the relationship between exposure to environmental stressors and the severity of thyrotoxicosis has not been well studied. Conversely, advanced age is associated with less severe Graves' hyperthyroidism, but the mechanism behind this observable fact is incompletely understood. The hypothesis of this study is that advancing age is associated with less exposure to stress, resulting in lower production of thyrotropin-binding inhibitory immunoglobulin (TBII), thus leading to less severe Graves' hyperthyroidism.

METHODS This is a cross-sectional observational study in which patients with an untreated initial episode of Graves' hyperthyroidism were recruited from nine participating centers in the Netherlands from July 2002 through September 2005. The inclusion criteria were a serum thyrotropin (TSH) level of <0.4 μIU/ml and a serum free thyroxine (FT_4) level of >23 pmol/L, with or without a serum triiodothyronine (T_3) level of >2.7 nmol/L, and with diffuse ^{99m}Tc-pertechnetate uptake on thyroid scintigraphy. Patients with a relapse of hyperthyroidism, verbal communication problems, or abuse of alcohol or drugs were excluded from the study. A variety of clinical features were recorded, including the hyperthyroidism symptoms score (HSS) and the presence of pretibial myxedema and Graves' ophthalmopathy. The HSS questionnaire quantitatively measures the clinical severity of hyperthyroidism using 10 items on 0- to 4-point subscale. Study participants completed two stress and one mood questionnaire at the time of diagnosis before treatment was initiated. Stress exposure was quantitated by three questionnaires: the Dutch questionnaire on stressful life events experienced in the past 12 months from a checklist of 60 possible events, which classifies the total amount of pleasantness and the total amount of unpleasantness, with a maximum score of 240 for each; the Dutch Everyday Problem Checklist, a validated version of the Daily Hassles Scale, which consists of 114 items concerning daily hassles experienced in the past 2 months; and the Positive and Negative Affect Schedule (PANAS) that measures a person's current mood, in terms of a positive and negative affect consisting of 22 mood states. Also measured were serum T_3, T_4, free T_4 index (FT_4I) and freeT_3 index (FT_3I), serum thyrotropin (TSH), and TBII. To analyze the influence of age on the severity of Graves' hyperthyroidism, patients were subdivided into four age groups: ≥29 years (n = 53), 30 to 39 years (n = 56), 40 to 49 years (n = 78), and ≥50 years (n = 76).

RESULTS The study subjects comprised 263 patients, 69 men (26%) and 194 women (74%), with a median age of 43 years (25th and 75th interquartile range, 32 to 51). The relationship between age and the biochemical severity of Graves' hyperthyroidism at the time of diagnosis is shown in Figure 1. Advanced age was associated with less severe biochemical hyperthyroidism (FT_3I and

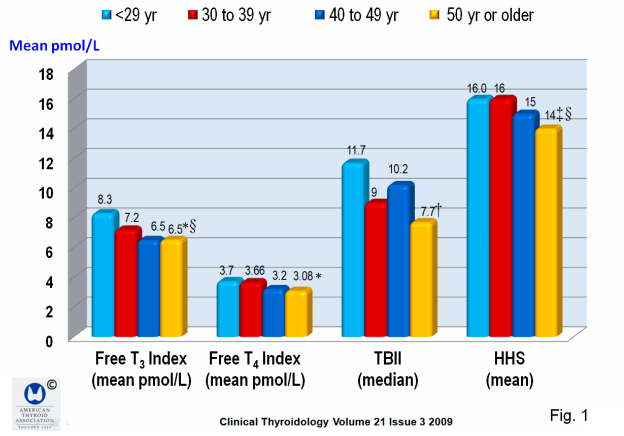

Figure 1. Values for serum FT_3I and FT_4I are pmol/L divided by 100. Advanced age was associated with less severe biochemical hyperthyroidism. *P<0.01 for FT_3I and FT_4I. †P = 0.05 for TBII. P = 0.07 for thyroperoxidase as compared with younger patients (data not shown). The clinical HSSs were significantly associated with less severe Graves' hyperthyroidism, ‡P = 0.04, with serum FT_3I (r = 0.028, §P<0.01). This figure is derived from data in Table 2 of Vox et al.

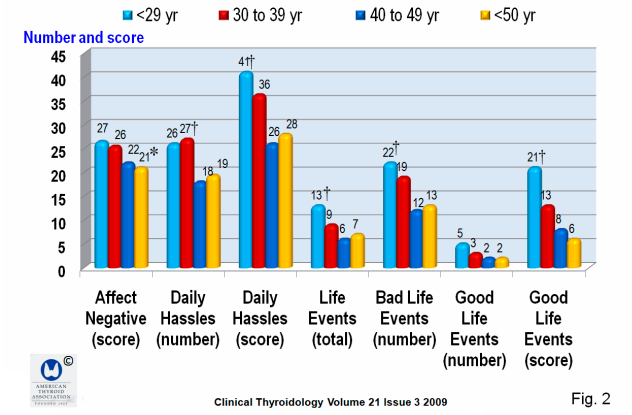

Figure 2. Age as determined for the amount of stress in 263 newly diagnosed patients with Graves' hyperthyroidism. Higher HSS scores were associated with higher frequencies and total scores for daily hassles, except for the intensity per hassle and the recently experienced stressful life event questionnaires. †P = 0.02. *P <0.01. The only other clinical characteristic associated with stress scores was goiter size, which positively correlated with both pleasantness and unpleasantness scores for recently experienced life event (P<0.01 and P = 0.01, respectively; data not shown). This figure is derived from data in Table 4 of Vox et al.

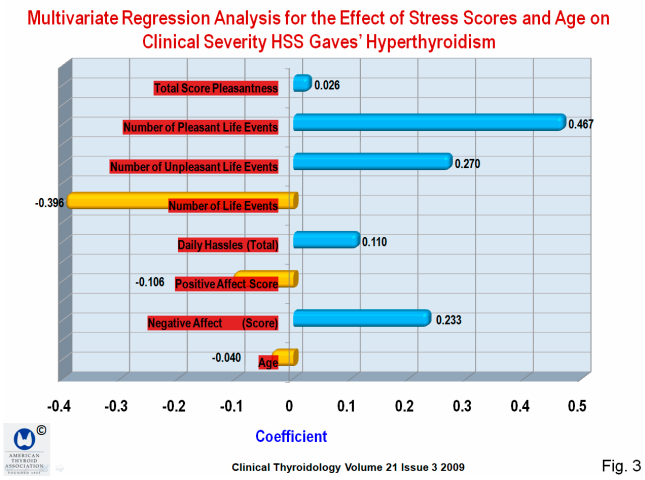

Fig. 3

Figure 3. Multivariate analysis showed that the clinical severity of Graves' hyperthyroidism was not related to age or the amount of stress exposure but was independently related to the tendency to report negative feelings (P<0.01).

FT_4I; P<0.01), and clinically less severe Graves' hyperthyroidism according to the HSS (P = 0.04). Trend analysis between different age groups showed that serum TBII and to a lesser extent, thyroperoxidase, were decreased with advancing age (P = 0.05 and P = 0.07, respectively). The HSS was significantly associated with serum FT_3I (r = 0.028, P<0.01) and to a lesser extent FT_4I (r = 0.017, P<0.01). Neither serum FT_4I, FT_3I, nor TBII was associated with PANAS scores; however, the total amount of pleasantness was directly associated with the FT_3I (P<0.01). Higher HSSs were associated with higher frequencies and total scores for daily hassles, except for the intensity per hassle and the recently experienced stressful life event questionnaires (Figure 2). The only other clinical characteristic associated with stress scores was goiter size, which positively correlated with both pleasantness and unpleasantness scores for recently experienced life events (P<0.01 and P = 0.01, respectively). Figure 2 shows the associations between age and various stress scores. Advanced age was associated with PNAS positive affect scores (P = 0.75) and with the frequencies of and total scores for daily hassles (P for trend, <0.01 for both), and with lower frequencies and scores for the recently experienced life events questionnaire (P<0.01). Multivariate analysis showed that the clinical severity of Graves' hyperthyroidism was not related to age or the amount of stress exposure but was independently related to the tendency to report negative feelings (P<0.01) (Figure 3).

CONCLUSION Although advancing age is associated with less exposure to stress and less severe clinical and biochemical tests of Graves' hyperthyroidism, these variables have no direct relationship to the severity of Graves' disease in older patients.

COMMENTARY

The relationship between the effects of age and clinical presentation of hyperthyroidism has intrigued clinicians and researchers for many years. While a number of studies, including the study by Vos et al. (1), have shown an age-related decrease in the degree of thyroid dysfunction in patients with Graves' disease, not all studies have shown this relationship (2, 3). The reasons usually given for the inverse relationship between age and thyroid dysfunction are decreased levels of TSAb in older patients, or a decreased responsiveness of thyrocytes to stimulation, or both. Furthermore, a decrease in serum T_3 that is well described in the "healthy" elderly is also likely operative in some older hyperthyroid patients as well (reviewed in 4), presumably due to occult comorbidity.

It has long been known that "older" people manifest fewer of the typical hyperthyroid symptoms than do their "younger" counterparts (5), but the reasons are uncertain. This is likely not related exclusively to the less deranged thyroid function in older individuals, given the statistically significant, but not terribly robust inverse relationship between thyroid function and symptoms noted by Vos et al. (1). Inspection of Figure 1 in their paper shows that Free T_3 and Free T_4 only accounted for a small part of the variability in the hyperthyroidism symptom score. It would have been interesting had the authors indicated in Figure 3 of their paper which patients were older and which were younger. Notably, others have shown major decreases in thyroid hormone action and responsiveness at the cellular level in aging animals and humans (6), which remain largely unexplained.

A relationship between stress and the onset of hyperthyroidism has been postulated beginning with the earliest case reports of Graves' disease. This connection has been documented in recent retrospective cohort studies (e.g., 7), and also in epidemiologic reports suggesting that stressful life events, such as war, can trigger the onset of Graves' disease in susceptible individuals (e.g., 8). How stress affects the immune system is uncertain, but may relate to altered circulating levels of glucocorticoids and/or catecholamines that influence the balance of cellular and humoral immunity (9).

In the paper by Vos et al. (1), the authors hypothesized that the milder biochemical abnormalities in hyperthyroid older persons might be due to less "stress" in their lives. Indeed, the authors did find that older persons lead less stressful lives. However, the degree of stress, as assessed by multiple validated instruments, was not related to the degree of thyroid dysfunction. Interestingly, however, one aspect of life stress, the negative affect score, was directly related in a statistically significant way to the hyperthyroid symptom score. Thus, patients whose mood tended to affect them in the most negative way tended to be more symptomatic when they became hyperthyroid.

The paper by Vos et al. (1) confirms the majority of studies showing that older hyperthyroid persons have fewer severe symptoms and less marked biochemical derangements than do younger patients. It is my feeling that this inverse relationship, while correct, only tells part of the story. The reasons underlying the decreased sensitivity of the elderly to the effect of thyroid hormone is a fundamental question in biology, and I hope that studies like this one will serve as an impetus to basic researchers to address this question in future studies.

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