Age and stress as determinants of the severity of hyperthyroidism caused by Graves’ disease in newly diagnosed patients

Xander G Vos, Natalie Smit, Erik Endert, Jan G P Tijssen and Wilmar M Wiersinga

Department of Endocrinology and Metabolism, F5-161, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands, Laboratory of Endocrinology, Department of Clinical Chemistry, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands, Division of Clinical and Health Psychology, Department of Psychology, Leiden University, Wassenaarseweg 52, 2333 AK, Leiden, The Netherlands and Division of Cardiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands

(Correspondence should be addressed to X G Vos; Email: x.g.vos@amc.nl)

Abstract

Objective: The evidence that stress may provoke Graves’ hyperthyroidism in genetically susceptible subjects is substantial. Whether exposure to stress is related to the severity of thyrotoxicosis has not been studied. Advancing age is associated with not only less severe Graves’ hyperthyroidism but also self-reported stress. We tested the hypothesis whether advancing age is associated with less exposure to stress, resulting in a lower immunological response, and less severe Graves’ hyperthyroidism.

Design: Cross-sectional multicenter study.

Patients: Two hundred and sixty-three consecutive untreated patients with a first episode of Graves’ hyperthyroidism were included. The severity of Graves’ hyperthyroidism was evaluated biochemically (freeT4-index and freeT3-index, thyrotropin-binding inhibitory immunoglobulin (TBII)) and clinically by the hyperthyroid symptom scale score (HSS score). Stress exposure was quantitated by three questionnaires.

Results: Advancing age was associated with less severe Graves’ hyperthyroidism, both biochemically by lower serum freeT3-index and freeT4-index (P < 0.01), lower serum TBII (P = 0.05), and clinically by lower HSS scores (P = 0.04) and smaller goiter size (P < 0.01). FreeT3-index and freeT4-index were directly associated with HSS scores (P < 0.01). Stress scores were associated with HSS scores (P < 0.01) but not with biochemical severity of Graves’ hyperthyroidism. Advancing age was associated with lower scores for stress exposure. Multivariate regression analysis showed that HSS score was independently related to the tendency to report negative feelings (P < 0.01) but not to other stress scores and also not to age.

Conclusion: Advancing age is associated with less exposure to stress, lower serum TBII and less severe clinical and biochemical Graves’ hyperthyroidism. Because no direct relationship exists between stress exposure and TBII or freeT3-index and freeT4-index, we reject our hypothesis that less stress is causally related to biochemically less severe Graves’ hyperthyroidism in old age. HSS score is primarily determined by negative feelings and not by age.

Introduction

Graves’ hyperthyroidism is a multifactorial disease with many predisposing genetic and environmental factors. Seventy-nine percent of the susceptibility to develop Graves’ hyperthyroidism can be attributed to genetic factors, leaving 21% for environmental factors (1). Exposure to stress, cigarette smoke, iodine excess, and several drugs have all been identified as relevant environmental factors in the pathogenesis of Graves’ hyperthyroidism. For example, since the first description by Parry of an association between a stressful life event and the occurrence of hyperthyroidism in 1825, many studies have reported a greater number of stressful life events in the year preceding the diagnosis of Graves’ hyperthyroidism when compared with controls (2–6). The evidence that environmental stimuli may provoke Graves’ hyperthyroidism in genetically susceptible subjects is rather good, but the quantitative relationship between the exposure to environmental stressors and the severity of the provoked thyrotoxicosis has scarcely been studied.

Age has consistently been observed as a significant modulating factor, advancing age being associated with less severe Graves’ hyperthyroidism (7–9). The mechanism behind less severe Graves’ hyperthyroidism in the older age groups is incompletely understood. Less severe Graves’ hyperthyroidism is due to lower levels of
thyrotropin-binding inhibitory immunoglobulin (TBII) (10). Furthermore, it has been shown that advancing age is associated with a decreased experience of self-reported stress (pleasant and unpleasant life events) (11). In turn, psychological stress has a differential effect on immune response, suppressing cellular and potentiating humoral immunity (12). We hypothesize that advancing age is associated with less exposure to stress, resulting in lower production of TBII and thereby in less severe Graves’ hyperthyroidism. To test this hypothesis, we performed a cross-sectional observational study in a large population of patients with newly diagnosed and untreated Graves' hyperthyroidism.

Subjects and methods

Study design

We included 263 consecutive untreated patients (69 males and 194 females, age 16–79 years at study entrance) with a first episode of Graves’ hyperthyroidism in a cross-sectional, multicenter, observational study. Patients were included from nine participating centers in the Netherlands from July 2002 until September 2005. Inclusion criteria were biochemical hyperthyroidism (TSH < 0.4 mU/l, fT4 > 23 pmol/l and/or T3 > 2.7 nmol/l) and a diffuse homogeneous uptake on thyroid scintigraphy (99mTc-pertechnetate). Exclusion criteria were relapse of Graves’ hyperthyroidism, no written informed consent, no understanding of the Dutch language, and serious alcohol or i.v. drugs abuse. Clinical parameters at baseline like sex, age, goiter size (classification by means of WHO 1960 criteria) (13), hyperthyroid symptom scale score (HSS score), and the existence of pretibial myxedema and Graves’ orbitopathy were recorded. Venous blood samples were taken for thyroid hormone measurements before treatment was started. The HSS score questionnaire (14) quantitatively measures clinical severity of hyperthyroidism through ten items on 0–4 point subscales, including sweating, heat intolerance, nervousness, hyperactivity, tremor, weakness, hyperdynamic precordium, diarrhea, appetite, and degree of incapacitation. Participants were asked to complete two stress and one mood questionnaires at time of diagnosis before treatment was started.

The study was approved by the local ethics committees of the Academic Medical Center of Amsterdam and the eight other participating centers. All patients gave written informed consent.

Stressful life event questionnaires

The Dutch questionnaire on recently experienced stressful life events (11) count the total number of major life events experienced in the past 12 months (checklist of 60 possible events). First, the respondent scores the amount of pleasantness for each experienced life event on a scale from 0 to 4. Second, the respondent scores the amount of unpleasantness for each experienced life event in a similar manner on a scale from 0 to 4. Third, the total amount of pleasantness and the total amount of unpleasantness are separately calculated by summing up all scores for pleasantness and unpleasantness respectively (maximal score 240 for each). Fourth, the total number of pleasant events is calculated by counting the number of life events in which the score for pleasantness exceeds the score for unpleasantness. The total number of unpleasant events is calculated in a similar manner in which the score for unpleasantness exceeds the score for pleasantness (maximum 60).

The Dutch everyday problem checklist, a validated version of the daily hassles scale (15, 16), consists of 114 items concerning daily hassles experienced in the last 2 months. It also measures the intensity of each hassle on a scale from 0 to 3, yielding the number of hassles experienced and the total intensity of these hassles (maximum 342).

The Positive and Negative Affect Schedule (PANAS) (17) measures the current mood, in terms of positive and negative affect. It consists of 22 mood states (11 positive and 11 negative) and the respondent is asked to report whether he/she is affected by each of these states on a scale from 1 (not at all) to 5 (a lot). This yields the tendency to report positive and negative affect states both on a scale from 11 to 55.

Laboratory measurements

Non-fasting venous blood samples were taken for thyroid hormone measurements and were stored at 20 °C until assay. Serum triiodothyronine (T3) and thyroxine (T4) were measured with in-house RIAs (18). T3 uptake was determined by a no extraction, solid phase 125I RIA (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA, USA). FreeT4-index and freeT3-index were calculated by multiplying T3 uptake with T4 and T3 respectively. Serum thyrotropin (TSH) was determined with a fluoroenzymometric assay (Delfia hTSH, Perkin Elmer, Turku, Finland; detection limit 0.01 mU/l). Serum TBII was quantitatively determined by a second generation luminescence receptor assay (TRAK human LIA, BRAHMS, Berlin, Germany; detection limit 1.0 IU/l). Autoantibodies against thyroid peroxidase (TPO-Ab) were analyzed by anti-TPOn LIA (BRAHMS; cutoff levels < 30 and > 3000 U/l). All measurements were performed at the laboratory of the Academic Medical Center of Amsterdam.

Statistical analysis

To analyze the influence of age on the severity of Graves’ hyperthyroidism, patients were subdivided into four groups; ≤ 29 years (N = 53), 30–39 years (N = 56),...
Table 1 shows the relationship between age and biochemical and clinical severity of Graves’ hyperthyroidism at the time of diagnosis. Advancing age was associated with both biochemically less severe Graves’ hyperthyroidism (freeT3-index and freeT4-index; \( P < 0.01 \)) and clinical less severe Graves’ hyperthyroidism as measured by HSS scores (\( P \) for trend = 0.04). Trend analysis showed that serum TBII and to a lesser degree TPO-Ab decreased with advancing age (\( P = 0.05 \) and \( P = 0.07 \) respectively).

The HSS score was significantly associated with serum freeT1-index (\( r = 0.28, P < 0.01 \)) and to a lesser extent with freeT4-index (\( r = 0.17 \), \( P < 0.01 \); Fig. 1).

Goiter size decreased with advancing age (\( P \) for trend < 0.01) (Table 2 and Fig. 2), while no association was found between age and the prevalence of orbitopathy and pretibial myxedema.

Table 3 shows the influence of stress scores on the biochemical and clinical severity of Graves’ hyperthyroidism. Neither serum freeT4-index, freeT3-index nor TBII were associated with PANAS scores, frequencies and total scores for daily hassles and recently experienced stressful life events questionnaires except for the total amount of pleasantness that was directly associated with freeT3-index (\( P \) for trend < 0.01). By contrast, higher HSS scores were related to more negative mood and less positive mood on the PANAS affect scores (\( P < 0.01 \)). Higher HSS scores were also associated with higher frequencies and total scores for daily hassles except for the intensity per hassle and the recently experienced stressful life event questionnaires (Table 3).

None of the other clinical characteristics were associated with stress scores, with the exception of goiter size being positively correlated to both pleasantness and unpleasantness scores for recently experienced life events (\( P < 0.01 \) and \( P = 0.01 \) respectively) (data not shown).

Table 4 shows the associations between age and various stress scores. Advancing age was associated with lower PANAS negative affect scores (\( P \) for trend = 0.02) but not with PANAS positive affect scores (\( P = 0.75 \)). With regard to daily hassles, the frequencies and total scores for daily hassles decreased with advancing age (\( P \) for trend < 0.01 and 0.01 respectively) while the intensity per hassle did not differ (\( P = 0.48 \)). Furthermore, advancing age was associated with lower frequencies and scores for the recently experienced stressful life events questionnaire (\( P < 0.01 \); Table 4).

To study the relationship between clinical severity (HSS score), age, and stress we performed multivariate regression analysis. The HSS score was used as dependent variable for all moods and stress scores (PANAS, The Dutch everyday problem checklist, and The Dutch questionnaire on recently experienced stressful life events) together with age (Table 5). This analysis showed that the clinical severity of Graves’ hyperthyroidism was not related to age nor to the...
amount of stress exposure but was independently related to the tendency to report negative feelings ($P < 0.01$).

Discussion

The first main finding of our study is that advancing age is associated with less severe Graves' hyperthyroidism (Table 2). Free $T_3$-index and free $T_4$-index are lower in the older age groups, as reported previously in several studies (7, 9, 19). Serum TBII also decreased with advancing age, again in agreement with the literature (7). Because TBII is directly related to free $T_3$-index and free $T_4$-index (10), the fall in serum TBII provides a satisfactory explanation of why the biochemical severity of Graves' hyperthyroidism decreases in older age. We also observed a decrease in the clinical severity of Graves' hyperthyroidism with age as evident from the fall in the HSS score. There was furthermore a shift toward smaller goiter size in elderly patients, a finding again explainable from the direct relationship between TBII and goiter size (10). Other studies also reported a lower frequency of symptoms and signs in elderly Graves' hyperthyroidism patients (notably less heat tolerance, less perspiration, less irritability, and less often increased appetite, tachycardia and goiter), although weight loss and atrial fibrillation are more common in old age (20-22). Clinical severity (HSS score) was directly related to the biochemical severity (free $T_3$-index and free $T_4$-index) of Graves' hyperthyroidism, but the correlation is weak (Fig. 1). Trzepacz et al.

![Figure 1](https://www.eje-online.org)

**Figure 1** Correlation between biochemical severity ([a] free $T_3$-index and [b] free $T_4$-index) and clinical severity (HSS score) of thyrotoxicosis in untreated Graves' hyperthyroidism.

![Figure 2](https://www.eje-online.org)

**Figure 2** Goiter size as a function of age (goiter size grade 0, thyroid not or distinctly palpable but usually not visible with head in a normal or raised position; grade I, thyroid easily palpable and visible with the head in either a normal or raised position; grade II, thyroid easily visible with the head in a normal position; grade III, goiter visible at a distance).
The second main finding of our study is that overall stress exposure is not related to the biochemical severity of Graves’ hyperthyroidism, but, by contrast, is directly related to the clinical severity (HSS score) of Graves’ hyperthyroidism (Table 3). Affect scores and stress from daily hassles or unpleasant recent life events were not related to freeT3-index and freeT4-index or to TBII; only higher amounts of pleasantness were significantly related to freeT3-index. By contrast, all stress parameters were associated with the clinical severity of Graves’ hyperthyroidism: higher negative affect or lower positive affect scores, and higher frequencies and scores for daily hassles and (un)pleasantness of recent life events were all associated with higher HSS scores. How can we explain the discrepancy that stress scores are only related to clinical severity and not to biochemical severity of Graves’ hyperthyroidism? When a person contracts a disease, his complaints to some extent will be influenced by his current mood state. If the person scores high on negative affects or low on positive affects, he/she is more likely to have complaints or to rate a particular complaint as more severe. Indeed, our studies did not observe a relationship between the HSS score and serum thyroid hormone concentrations in newly diagnosed untreated Graves’ hyperthyroidism patients (23), most likely due to the low sample size (n = 25) in their study.

The third main finding of our study is that advancing age is associated with less exposure to stress (Table 4). The frequency and total amount of unpleasantness or pleasantness experienced from stressful life events in the year preceding the diagnosis of Graves’ hyperthyroidism decreased in the older age groups, and the same was true for the frequency and total intensity of daily hassles of the last months. The current mood state of elderly patients was also better, because they were less influenced by negative affects. These interesting observations are in line with studies from the field of...
Recently experienced stressful life events

Everyday problem checklist

Positive and negative affect schedule (PANAS)

reflects the influence of cumulative exposure to foreign pathogens over time. It means that advancing age is associated with a lack of clonotypic immune response to antigens.

Going back to our hypothesis we can conclude that advancing age is indeed associated with less exposure to stress, lower serum TBII and less severe clinical and biochemical Graves’ hyperthyroidism. Because no direct relationship existed between stress exposure and TBII or freeT₃-index and freeT₄-index, we reject our hypothesis that less stress is causally related to biochemically less severe Graves’ hyperthyroidism in old age. We find the observed tendency to higher freeT₃-index with higher amounts of total pleasantness insufficient evidence to support our hypothesis in view of all other findings. Because the extent to which patients express complaints are influenced by many factors including current mood state, we prefer freeT₃-index and freeT₄-index as objective measures for the severity of Graves’ hyperthyroidism.

Table 4 Age as determinant for the amount of stress in 263 newly diagnosed patients with Graves’ hyperthyroidism.

<table>
<thead>
<tr>
<th></th>
<th>≤29 years (N=53)</th>
<th>30–39 years (N=56)</th>
<th>40–49 years (N=78)</th>
<th>≥50 years (N=76)</th>
<th>P value (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive and negative effect schedule (PANAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative affect score</td>
<td>26.5 (18.2–0.0)</td>
<td>25.5 (18.2–31.8)</td>
<td>22.0 (17.0–28.0)</td>
<td>21.0 (16.0–26.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Positive affect score</td>
<td>38.5 (33.2–41.0)</td>
<td>37.5 (32.2–41.0)</td>
<td>38.5 (33.0–43.0)</td>
<td>38.0 (33.0–40.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Everyday problem checklist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of daily hassles</td>
<td>26.0 (17.0–40.0)</td>
<td>27.0 (12.0–39.0)</td>
<td>18.0 (10.5–28.9)</td>
<td>19.4 (10.0–29.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intensity per hassle</td>
<td>1.6 (1.3–1.9)</td>
<td>1.6 (1.2–1.9)</td>
<td>1.6 (1.2–2.0)</td>
<td>1.8 (1.1–2.1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Daily hassles total score</td>
<td>41.0 (22.0–69.0)</td>
<td>38.3 (16.0–63.0)</td>
<td>26.0 (13.0–48.5)</td>
<td>28.0 (9.0–48.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Recently experienced stressful life events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of life events</td>
<td>13.0 (7.0–20.0)</td>
<td>9.0 (7.0–15.0)</td>
<td>6.0 (4.0–10.5)</td>
<td>7.0 (4.0–12.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of unpleasant life events</td>
<td>7.0 (3.0–10.0)</td>
<td>6.0 (3.0–11.0)</td>
<td>4.0 (2.0–7.0)</td>
<td>4.0 (2.0–7.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total score unpleasantness</td>
<td>22.0 (11.0–44.0)</td>
<td>19.0 (10.0–38.0)</td>
<td>12.0 (6.0–19.0)</td>
<td>13.0 (4.0–23.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of pleasant life events</td>
<td>5.0 (3.0–10.0)</td>
<td>3.0 (1.0–6.0)</td>
<td>2.0 (1.0–3.0)</td>
<td>2.0 (0.0–3.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total score pleasantness</td>
<td>21.0 (11.0–30.0)</td>
<td>13.0 (7.0–22.0)</td>
<td>8.0 (3.5–11.5)</td>
<td>6.0 (2.5–11.0)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are given as median + interquartile range (between parentheses).

Table 5 Multivariate regression analysis for the effect of stress scores and age on clinical severity (HSS score) of Graves’ hyperthyroidism.

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>13.896 (4.036)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>-0.041 (0.040)</td>
<td>0.307</td>
</tr>
<tr>
<td>Positive and negative affect schedule (PANAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative affect score</td>
<td>0.233 (0.067)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Positive affect score</td>
<td>-0.106 (0.065)</td>
<td>0.106</td>
</tr>
<tr>
<td>Everyday problem checklist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of daily hassles</td>
<td>0.110 (0.083)</td>
<td>0.187</td>
</tr>
<tr>
<td>Intensity per hassle</td>
<td>-0.508 (1.187)</td>
<td>0.669</td>
</tr>
<tr>
<td>Daily hassles total score</td>
<td>-0.030 (0.051)</td>
<td>0.548</td>
</tr>
<tr>
<td>Recently experienced stressful life events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of life events</td>
<td>-0.396 (0.467)</td>
<td>0.398</td>
</tr>
<tr>
<td>Number of unpleasant life events</td>
<td>0.271 (0.583)</td>
<td>0.643</td>
</tr>
<tr>
<td>Total score unpleasantness</td>
<td>0.044 (0.121)</td>
<td>0.715</td>
</tr>
<tr>
<td>Number of pleasant life events</td>
<td>0.467 (0.535)</td>
<td>0.384</td>
</tr>
<tr>
<td>Total score pleasantness</td>
<td>0.026 (0.184)</td>
<td>0.890</td>
</tr>
</tbody>
</table>

Standard error (between parentheses).

Acknowledgements

We gratefully thank the participating physicians for their collaboration in this study: Dr A B Arntzenius (Sparnaar Ziekenhuis, Hoofddorp), Dr C B Brouwer (Onze Lieve Vrouwe Gasthuis, Amsterdam), Dr J Derksen (Medisch Spectrum Twente, Enschede), Dr M J M Diekman, and Dr M N Gerding (Ziekenhuis Deventer, Deventer), Dr V E A Gerdes (Slotervaartziekenhuis, Amsterdam), Dr W E de Graaff (Tergooiziekenhuizen, Blaricum), Dr R Heijligenberg (Ziekenhuis Gelderse Vallei, Ede), and Dr A F Muller (Diakonessenhuis, Utrecht). We would like to thank Ms E M Johannesma for all laboratory measurements.
References


Received 9 October 2008
Accepted 27 October 2008