Graves’ disease, endocrine ophthalmopathy and smoking

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Graves’ disease is an autoimmune disorder of the thyroid gland in which thyroid stimulating antibodies are produced and lead to an excessive output of thyroid hormones. The disease is associated with endocrine ophthalmopathy in many of the patients (1). The etiology of Graves’ disease is multifactorial. Heredity and sex are of importance (2–4) as well as environmental factors such as negative life events and divorces (5). Viral infections have also been postulated as possible etiological factors (4, 6). In a small number of Graves’ disease patients, endocrine ophthalmopathy present at onset may progress or develop and severe eye disease may occur during the course of treatment. An activation of the thyroid gland via the TSH receptor seems to be of importance in such a development (7). The etiology of endocrine ophthalmopathy, however, remains obscure and, although autoimmunity is generally thought to play a role, no specific ocular antigen has been identified (8). Hägg and Asplund (9) first reported on a possible association between eye disease and smoking, a finding which has later been confirmed by others (10, 11). These studies have been retrospective and based on selected patients with manifest endocrine ophthalmopathy. A recently published study by Tellez et al. (12) not only confirmed the association to smoking but also reported on an ethnic difference in the prevalence of endocrine ophthalmopathy in patients with Graves’ disease, with Asians having a significantly lower risk of developing endocrine ophthalmopathy compared to Europeans.

In the present study, we evaluated the association between smoking, Graves’ disease and endocrine ophthalmopathy in a prospective, case-control study of a Swedish population and also carried out a retrospective survey of a referred group of patients with severe endocrine ophthalmopathy.

Subjects and methods

Two hundred and eight patients (out of 219) with newly diagnosed Graves’ disease admitted to four county hospitals in central Sweden during a two-year period were included in the study. Diagnosis was based on clinical signs, elevated thyroid hormone levels and suppressed thyrotropin. Triiodothyronine (T3) and thyroxine (T4) were measured by solid phase radioimmunoassays (reference values: T3: 1.2–2.8 nmol/l, T4: 67–153 nmol/l). Thyroxine binding proteins were estimated as T3U (75–115%) by the ‘Phadebas T3U Test’ (Pharmacia, Uppsala, Sweden) and thyrotropin (TSH) was measured by a radioimmunosorbent technique (< 5 mU/l). Total T4 and T3U values were used to calculate an FT4 index in 164 of the patients. In the remaining 44 sera the thyroxine-binding proteins were measured with a different method and these sera were not included in...
the analysis of FT$_4$-I, TSH-receptor antibodies (TRAb), measured by a radioreceptor binding assay (TRAK, Henning, Berlin, Germany) were found in 178 of the patients (8 values absent). Undetectable TSH-receptor antibodies in patients with Graves’ disease have recently been described (13). In the present study, 22 patients had no thyrotropin receptor antibodies but had clinical signs typical of Graves’ disease. Antibodies against thyroid peroxidase (TPO-Ab), thyroglobulin (Tg-Ab) and gastric H,K-ATPase were determined by enzyme-linked immunosorbent assays (14, 15).

One experienced clinician at each hospital examined the patients, who were asked specifically about eye symptoms and these were noted in 206 cases. Clinical signs of eye disease were evaluated by the clinician. Based on symptoms and signs, the endocrine ophthalmopathy was graded as mild (I) with increased teariness, increased irritability, lid retraction, moderate (II) with mild signs and/or periorbital swelling, conjunctival injection, proptosis, impaired motility, severe (III) with grade II eye signs and double vision, pain upon eye movement and/or marked proptosis (findings which we consider require corticosteroid therapy) or malignant (IV) with grade III eye signs and optic nerve affection, reduced visual acuity and/or visual field defects. The patients received different forms of treatment. Sixty-nine patients received only thyreostatic drugs for a mean duration of 30.1 months. Eighty-eight patients were treated with radioiodine, of these 29 were medically pretreated. Forty-seven patients were operated and 37 of these were pretreated with thyreostatic drugs for less than six months prior to operation and the remaining 10 patients received medical treatment for a mean of 35.0 months and were then operated since the medical treatment was considered insufficient. Two patients received no treatment. The patients were followed during and after treatment, with a mean follow-up of 34 months (sd ± 15.5, range 4–60), during which any signs of eye disease were noted. Forty-six patients were not monitored by their clinician when the therapy proved successful. They were contacted by telephone in order to complete a history of their eye symptoms. All patients completed a questionnaire immediately after their referral to the hospital. For each patient, two controls, matched for sex, age and county residence, were randomly selected (5). Three-hundred-and-seventy-two controls (80%) replied and among the 91 non-responders, 39 did not give a reason for not answering and were not possible to get hold of; 21 did not answer because they were afraid to have their names on a register. 17 declined to take part but did not want to explain why. 9 found the questions too personal. 3 questionnaires were lost in the mail, 1 person was too ill to take part and 1 did not fill in the form correctly. The questionnaires consisted of 95 items (see (5)) concerning different exposures. Among these were questions on smoking habits (current or former, the number of cigarettes smoked daily: ≤ 10 or > 10, other forms of tobacco such as snuff, pipe tobacco, changes in smoking habits during the last years) and drinking habits. "Persons with a history of smoking" comprised all current as well as former smokers (ever-smokers). The study was approved by the local ethics committee of the University Hospital, Uppsala.

In a separate retrospective study of 72 patients with Graves’ disease admitted to our ward from 1985 to 1991 due to endocrine ophthalmopathy, tobacco use was also elucidated. The patient material consisted of three groups with different levels of endocrine ophthalmopathy severity. Twenty-two patients had moderate endocrine ophthalmopathy (grade II) but did not require any other treatment than thyreostatic drugs. Thirty-three patients had severe endocrine ophthalmopathy (grade III) and were given additional treatment with corticosteroids. Fifteen patients belonged to the group with the most severe endocrine ophthalmopathy, i.e. impaired visual acuity, and were classified as malignant (grade IV).

Statistics

Chi-square and Student’s t-tests (two-tailed) were used to study differences between the groups. The association was also expressed as odds ratio (OR) with 95% confidence limits, as a measure of the relative risk.

Results

In the prospective study of 208 patients with newly diagnosed Graves’ disease, the cases smoked significantly more than their healthy controls. As regards current smokers, there were 41% smokers in the patient group compared with 30% in the control group (p < 0.01, OR 1.6, 95% CI 1.1–2.3), and when previous smoking habits were also considered, there were 51% cases with a history of smoking (ever-smokers) among the patients and 42% among the controls (p < 0.05, OR 1.4, 95% CI 1.0–1.9) (Table 1).

Signs of endocrine ophthalmopathy at the time of diagnosis were found among 62 of the 206 patients (30%) and of these 39 (19%) had mild disease and 23

| Table 1. Frequency of smokers among Graves' disease patients with and without endocrine ophthalmopathy (EO) and healthy controls. |
|--------------------------------------------------|--------|--------|
| Cases                                           | 208    | 41%    | 51%    |
| Controls                                        | 372    | 30%$^c$| 42%$^b$|
| Cases with EO                                   | 62     | 48%    | 63%    |
| Cases without EO                                | 142    | 38%$^c$| 45%$^d$|

$^a$p < 0.01 vs cases; $^b$p < 0.05 vs cases; $^c$p = 0.17 vs cases with EO; $^d$p < 0.05 vs cases with EO.
(11%) had moderate disease. Forty-nine of the 62 cases with endocrine ophthalmopathy were women and 13 (21%) were men. This ratio did not differ from the distribution of the sexes in the total Graves’ disease material where 18% of the patients were men (p = 0.46).

Analysis of the smoking status revealed that there were not more current smokers among patients with eye signs compared with Graves’ disease patients without eye symptoms (48% vs 38% smokers, p = 0.17). This analysis tended to be an association if only women were included (p = 0.06). When the analysis was made for patients with a smoking history, there was a weak but significant association between smoking and eye signs. Sixty-three percent of the patients with eye symptoms had a history of smoking compared with 45% of the patients without eye signs, giving a p value of <0.05 (OR 2.1 95% CI 1.1–3.9). This association also appeared stronger in the case of women (p < 0.01).

Patients with symptoms of endocrine ophthalmopathy had a greater FT4 index (p < 0.05) (Table 2). Their T3 levels were also higher but did not reach statistical significance (p = 0.057). The thyrotropin-receptor antibody levels were higher in the group with eye signs (p < 0.05). No differences between the groups were found as regards antibodies against thyroid peroxidase, thyroglobulin and the parietal cell antigen (H-K-ATPase). When current smokers or patients with a smoking history were compared with non-smokers there were no differences in any of the parameters analyzed.

Thirteen patients (6.4%) developed mild to moderate endocrine ophthalmopathy during treatment and at follow-up and of these nine had received radioiodine alone (N = 5) or in combination with thyreostatic drugs (N = 4). Three patients were on medication only and one received drugs but was later operated. Nine of these 13 patients were non-smokers and four were smokers. Fourteen patients (6.9%) with endocrine ophthalmopathy at diagnosis developed more severe eye disease at follow-up (radioiodine only: 3 patients, radioiodine + thyreostatic drugs: 2 patients, drugs only: 5 patients, drugs + surgery: 4 patients). There were 7 non-smokers and 7 smokers in this group of patients.

In the retrospective material of 72 patients undergoing treatment for Graves’ disease and having endocrine ophthalmopathy upon referral to our unit, we found that 64% of the patients with moderate endocrine ophthalmopathy were smokers. Among patients with severe endocrine ophthalmopathy administered steroid treatment there were 71% smokers and in the group of 15 patients without impaired visual acuity due to malignant endocrine ophthalmopathy, the percentage of smokers was 87% (Table 3). In all, there were 17 men (24%) in this retrospective material with 6/22 (27%), 7/35 (20%), and 4/15 (27%) men in the two subgroups, respectively. For comparison, the prevalence of current smokers in the total Swedish population was 27% for men and 26% for women during the 1980s. The corresponding figures for persons with a smoking history were 57% and 45% according to the Central Bureau of Statistics in Sweden (unpublished material).

**Discussion**

Our inquiry into smoking habits in the prospective case-control study enabled us to elucidate that smoking is associated with an increased risk of developing Graves’ disease. The etiology of this disorder is largely unknown but considered to be multifactorial. Gender is apparently

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**Table 2. Characteristics of 208 patients with newly diagnosed Graves’ disease included in the prospective case-control study. EO: endocrine ophthalmopathy.**

<table>
<thead>
<tr>
<th>Cases</th>
<th>With EO</th>
<th>W/o EO</th>
<th>p</th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)a</td>
<td>44 ± 12</td>
<td>47 ± 15</td>
<td>n.s.</td>
<td>44 ± 12</td>
<td>47 ± 15</td>
<td>n.s.</td>
</tr>
<tr>
<td>Malesb</td>
<td>21%</td>
<td>17%</td>
<td>n.s.</td>
<td>16%</td>
<td>20%</td>
<td>n.s.</td>
</tr>
<tr>
<td>T4 (nmol/l)a</td>
<td>6.6 (4.3–10.3)</td>
<td>4.9 (4.3–8.3)</td>
<td>n.s.</td>
<td>6.2 (4.2–9.2)</td>
<td>6.1 (4.3–8.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FT41p</td>
<td>322 (220–472)</td>
<td>277 (195–392)</td>
<td>p &lt; 0.05</td>
<td>285 (194–418)</td>
<td>290 (206–410)</td>
<td>n.s.</td>
</tr>
<tr>
<td>TRAb positiveb</td>
<td>95%</td>
<td>88%</td>
<td>n.s.</td>
<td>88%</td>
<td>90%</td>
<td>n.s.</td>
</tr>
<tr>
<td>TRAb titer (U/l)p</td>
<td>47 (14–155)</td>
<td>32 (12–88)</td>
<td>p &lt; 0.05</td>
<td>33 (12–93)</td>
<td>38 (12–116)</td>
<td>n.s.</td>
</tr>
<tr>
<td>TPO-Ab positiveb</td>
<td>86%</td>
<td>85%</td>
<td>n.s.</td>
<td>87%</td>
<td>84%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Tg-Ab positiveb</td>
<td>26%</td>
<td>25%</td>
<td>n.s.</td>
<td>20%</td>
<td>28%</td>
<td>n.s.</td>
</tr>
<tr>
<td>H,K-ATPase</td>
<td>Ab positiveb</td>
<td>35%</td>
<td>31%</td>
<td>n.s.</td>
<td>38%</td>
<td>31%</td>
</tr>
</tbody>
</table>

a Mean values ± s.d compared with unpaired t-test. Analysis of the T4, FT4 and antibody data was performed after logarithmic transformation which normalized their distribution.

b The frequency is given as the percentage of each group after comparison using chi-square tests.

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**Table 3. Frequency of smokers among the 72 patients with endocrine ophthalmopathy (EO) in the retrospective study.**

<table>
<thead>
<tr>
<th>Cases</th>
<th>N</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate EO</td>
<td>22</td>
<td>64%</td>
</tr>
<tr>
<td>Severe EO</td>
<td>35</td>
<td>71%</td>
</tr>
<tr>
<td>Malignant EO</td>
<td>15</td>
<td>87%</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

The prevalence of current smokers in the total Swedish population was 27% for men and 26% for women during the 1980s. The corresponding figures for persons with a smoking history were 57% and 45% according to the Central Bureau of Statistics in Sweden (unpublished material).
important since the female to male ratio of the disease is at least 5:1 (4). Heredity is of importance (2, 3) and we have recently published a study indicating that stress, in the form of negative life events, has an influence in eliciting the disease (5). The risk estimates for heredity were 3.6 and for negative life events 6.3 (5). Thus the association to smoking found in the present study is comparatively weak with an odds ratio of 1.5.

The mechanism by which smoking could constitute a risk is not apparent. It might directly affect thyroid function or have immunological or other as yet poorly defined effects. The prevalence of goiters is higher among smokers than non-smokers (16, 17) and smokers have been found to have both higher T3 (17) and similar T4 (16) levels as non-smokers. Lower TSH values have been found among male but not female smokers (16, 17). Since smoking did not influence thyroid hormone or TSH values in the patients in our prospective study when Graves’ disease was diagnosed, we consider smoking unlikely to affect thyroid function per se. The effect of smoking on the immune system as well as on the course of immunological diseases has been studied extensively but with conflicting results (18–20). Smoking influences both humoral (21) and cellular immunity (22) and has been suggested to have an immunosuppressive effect based on for example reports of a negative correlation between smoking and ulcerative colitis (23, 24)—a disease with a possible immunological etiology—with a clustering of disease onset after termination of smoking (25, 26). This negative association was not seen in another autoimmune disease, viz. SLE (20), and conflicting data concerning the relation between smoking and rheumatoid arthritis have been published (19, 27).

No association has been found between smoking and autoimmune thyroiditis (16, 28) with the exception of a weak association in a study of women with postpartum thyroiditis (29). In our prospective case control study of Graves’ disease, no effect of smoking on TSH receptor or thyrogastric autoantibody levels was detected. Thus, there are little data to support an immunological role of smoking in Graves’ disease.

Endocrine ophthalmopathy is associated to Graves’ disease, and a majority of the patients with the eye disease have had or have ongoing thyrotoxicosis (1, 8). Here too, the etiologic factors are largely unknown and the efforts to identify an ocular antigen have so far proved unsuccessful (8). Many patients with Graves’ disease have mild signs of endocrine ophthalmopathy at the time of diagnosis. In the majority of the patients, the symptoms resolve, but in a minority severe endocrine ophthalmopathy develops. Some patients develop endocrine ophthalmopathy once the therapy has begun, in some cases long after the Graves’ disease has been diagnosed. The pathogenetic mechanism is not known but the mode of treatment seems to be of importance.

Thus, radioactive therapy has been found to be associated with the greatest increase in the risk of developing endocrine ophthalmopathy when compared with thyrostatic drugs or thyroid surgery (7, 30). In the present case-control study 14/88 (16%) of the patients who developed or progressed in endocrine ophthalmopathy had been given radioiodine, in comparison to 8/69 (11%) and 5/47 (11%) of patients treated with thyrostatic drugs or surgery, respectively. The material was too small to allow for statistical analyses on the association between radioiodine and endocrine ophthalmopathy. An activation of the thyroid gland via the TSH receptor, caused either by TSH elevations due to treatment-induced hypothyroid episodes or by increasing levels of TSH receptor antibodies, a phenomenon typically found following radioiodine therapy (4, 31, 32), has been suggested as a common denominator among cases who develop severe endocrine ophthalmopathy during Graves’ disease treatment (7).

The clinical observation of an increased number of smokers among patients with severe endocrine ophthalmopathy has been confirmed by studies published during recent years (10–12). Most of these studies have been retrospective and have been performed on patients with already apparent endocrine ophthalmopathy. Our clinical impression is in accordance with these previous observations and the results of our retrospective survey give further support to the association. It thus appears that in a patient undergoing treatment for Graves’ disease with, for poorly understood reasons, an ongoing and progressive eye disease, smoking enhances the disease process and greatly increases the risk of severe endocrine ophthalmopathy. No evidence of an immunological basis for this development exists and, presumably, the influence of smoking at this stage could be due to a more direct, locally inflammatory effect.

In conclusion, our results reveal that smoking is a risk factor in Graves’ disease and is not strongly associated to eye disease at the time of diagnosis. Persistent smoking, however, once treatment has begun, greatly increases the risk of developing severe endocrine ophthalmopathy, and for this reason we encourage the patients with Graves’ disease to stop smoking in order to avoid endocrine ophthalmopathy, the most severe complication of Graves’ disease.

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References

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