Multi-center study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy experience

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Abstract

To improve management of patients with Graves' orbitopathy, a multi-center collaborative approach is necessary in order to have large enough sample sizes for meaningful randomized clinical trials. This is hampered by a lack of consensus on how to investigate the eye condition. The European Group on Graves' Orbitopathy aims to overcome this and has designed a preliminary case record form (CRF) to assess Graves' orbitopathy patients. This form was used in this first multi-center study.

Aim: To investigate patient characteristics and treatment strategies in 152 new consecutively referred patients with thyroid eye disease seen in nine large European referral centers.

Methods: Newly referred patients with Graves' orbitopathy were included who were seen between September and December 2000. Demographic data and a complete ophthalmological assessment were recorded.

Results: One-hundred and fifty-two patients (77% females) were included. Diabetes was present in 9%, and glaucoma or cataract in 14% of patients. Forty percent were current smokers, 9% also had dermopathy, and only 33% reported a positive family history of thyroid disease. Mild eye disease was seen in 40%, moderately severe eye disease was seen in 33% and severe eye disease was seen in 28% of patients. Soft tissue involvement was the most frequent abnormality (seen in 75%), proptosis $\geq 21$ mm was found in 63%, eye motility dysfunction in 49%, keratopathy in 16% and optic nerve involvement was found in 21% of patients. According to the clinical impression, 60% had active eye disease. Immunosuppressive treatment was planned more frequently in active patients (57/86; 66%) than in inactive patients (5/57, 9%; Chi-square 46.16; $P < 0.02$). There were no important differences among the eight centers regarding the severity and the activity of their patients.

Conclusions: In view of the large number of patients recruited in only 4 months, multi-center studies in the eight EUGOGO centers appear to be feasible.
between orbital surgeons and endocrinologists. The first effort of this group was to reach some consensus on how to assess the eye changes; this resulted in the establishment of a preliminary case record form (CRF) to be used to assess both the severity and the activity of the thyroid-associated eye disease. The usefulness of this CRF was tested in this first multi-center study. The aims of this cross-sectional study were to investigate the variation in patient characteristics and treatment choice in 152 consecutive, newly referred patients among the eight participating centers.

Methods

We included newly referred patients with Graves’ orbitopathy during a 4-month period in 2000. All patients were assessed using the newly developed, 13 page long CRF, which included several general demographic questions and an extensive inventory regarding the severity and the activity of the eye disease. The completed CRFs were then sent to the Amsterdam center and analyzed using the SPSS software package (SPSS Inc., Chicago, IL, USA).

General demographic characteristics

The duration of the eye disease and of the thyroid disease (in months) were recorded in two ways: (i) the time elapsed since the onset of the disease as perceived by the patient, and (ii) the time since a diagnosis was made by a physician.

Assessment of disease severity

Eye signs were assessed using various well established methods according to local preferences (5). In order to compare the results in the different centers, consensus was reached during a EUGOGO meeting to include a number of assessment methods to be used in all centers. The newly developed color atlas (6) was used to get a more reliable assessment of several subjective, but important symptoms of orbitopathy. For all NOSPECS (7) categories at least one assessment was selected. NOSPECS class 2 (soft tissue involvement) was assessed using the color atlas (6). In addition, the lid aperture (in mm) was measured at the midline in primary gaze. NOSPECS class 3 (proptosis) was assessed using a Hertel exophthalmometer. Eye muscle involvement (NOSPECS class 4) was assessed using the Bahn and Gorman diplopia score (8). NOSPECS class 5 (corneal involvement) was assessed using the color atlas. For NOSPECS class 6 (sight loss due to optic nerve involvement) we measured visual acuity using the decimal system, and optic nerve involvement was defined to be present if there was disc swelling or pallor, a visual field defect, or if visual acuity was less than 0.63 in the absence of other reasons for sight loss.

To be able to reach a meaningful interpretation of the treatment plans, patients were arbitrarily divided into three categories of severity. For this study, mild disease was defined as minimal to moderate soft tissue swelling, proptosis < 25 mm, no or only intermittent diplopia, no corneal or optic nerve involvement. Moderate disease was defined as marked soft tissue swelling, and/or proptosis ≥ 25 mm, and/or inconstant diplopia, and/or punctate staining of the cornea, but no optic nerve involvement. Severe eye disease was defined as constant diplopia and/or optic nerve involvement. In addition, the total eye score (TES) was calculated from the data submitted (9). In short, each NOSPECS class is multiplied by the grade in that class (a being substituted by 1, b by 2, c by 3) and the sum of the scores constitutes the TES.

Assessment of disease activity

This was carried out using the clinical activity score (CAS) (10), but physicians were also asked for their overall clinical impression as to whether the patient was thought to have active or inactive disease. The CAS consists of seven items and one point is added for each item present: spontaneous pain behind the globe, pain on attempted upgaze, redness of the conjunctiva, redness of the eyelid, chemosis, swelling of the caruncle, and eye lid swelling. For this, physicians could also use local imaging techniques such as the T2 relaxation time on MRI, or the orbital octreotide uptake on scintigraphy (11, 12).

Treatment plan

At the end of the first evaluation(s), the physician was asked to record the immediate first treatment plan. If various therapies were thought to be necessary (decompression followed by eye muscle surgery), only the first treatment option was recorded.

Differences among centers were tested only for those centers which included at least 15 patients. Testing was carried out by Pearson Chi-square tests, or ANOVA, or Kruskal–Wallis tests where appropriate. Where values are missing, data are reported as percentage of the number of patients in whom a specific item was assessed.

Results

One-hundred and fifty-two CRFs were returned from eight participating centers (Table 1), and the general demographic data are reported in Table 2. Of all patients only 7 (5%) were not caucasian. Thirty-three percent reported a family history of autoimmune thyroid diseases, and 12% had family members with other autoimmune diseases. Other eye diseases (cataract, glaucoma) were present in 14%, and as many as...
9% of the patients also had diabetes mellitus. Hyperthyroidism was mostly treated with antithyroid drugs, but 30% of the patients had received radioactive iodine. The latter treatment was more often applied in the UK than in the other countries (55% vs 19%; \( P < 0.001 \)).

In our cohort, 75% of the patients had at least NOS-PECS class 2 signs (upper eye lid swelling being more frequent than lower eye lid swelling), 38% qualified for class 3 (proptosis \( \geq 23 \) mm), but 63% of the patients had values above the upper normal limit of 20 mm (2); 49% had class 4 signs (eye muscle involvement), 16% had class 5 signs (corneal damage), and 21% had signs of optic nerve involvement compatible with class 6 (Table 3). Regarding keratopathy, only patients with mild keratopathy were encountered. Although a visual acuity of less than 0.8 was seen in 28% of patients, true optic nerve involvement was slightly less frequent. Choroidal folds were seen in only one patient, a relative afferent pupillary defect was found in two patients, and a pale optic disc was seen in three patients. Apical crowding on CT-scan was found in 11 patients, of whom four had clinical evidence of optic nerve involvement.

Most patients (40%) had milder forms of ophthalmopathy, whereas 33% had moderate and 28% had severe eye disease (Table 3). Diplopia was absent in 51% of patients, and 15% had intermittent, 20% had constant and 14% had constant double vision. The elevation was abnormal in 49%, the abduction in 32%, and the depression in 17% of patients. There were no differences in disease severity among the patients seen by the various centers.

The majority (68%) of our patients had not yet received any specific therapy, except for local measures such as eye drops, which were being used by 51% of the patients. Corticosteroids were already used by 28% of the patients, whereas 9% had been irradiated and 11% had undergone some form of rehabilitative surgery in another center.

Table 1 Number of patients newly referred to the different EUGOGO centers between September and December 2000.

<table>
<thead>
<tr>
<th>Center no.</th>
<th>Name</th>
<th>Country</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Academic Medical Center, Amsterdam</td>
<td>Netherlands</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>University Medical Center, Utrecht</td>
<td>Netherlands</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>The Newcastle-upon-Tyne Hospitals</td>
<td>UK</td>
<td>27</td>
</tr>
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<td>4</td>
<td>University of Wales College of Medicine</td>
<td>UK</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Joh Gutenberg Klinikum, Mainz</td>
<td>Germany</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>Centre Hospitalier, Lyon-Sud</td>
<td>France</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>University of Pisa</td>
<td>Italy</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>Panagia General Hospital, Thessaloniki</td>
<td>Greece</td>
<td>41</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>152</strong></td>
</tr>
</tbody>
</table>

Table 2 General characteristics of all (\( n = 152 \)) newly referred patients seen in eight EUGOGO centers between September and December 2000.

- **Age in years (mean±s.d.)**: 49±13
- **No. of females**: 117/152 (77%)
- **No. of current smokers**: 60/150 (40%)
- **No. of patients with dromopathy**: 9/133 (6%)
- **No. of patients with hyperthyroidism**: 142/152 (93%)
- **No. of patients with hypothyroidism**: 6/152 (4%)
- **No. of patients without thyroid dysfunction**: 4/152 (3%)
- **No. of patients with a family history of Autoimmune thyroid disease**: 46/139 (33%)
- **Other autoimmune diseases**: 16/139 (12%)
- **No. of patients with relevant comorbidity**
  - Glaucoma or cataract: 20/141 (14%)
  - Diabetes: 12/141 (9%)
  - Other autoimmune diseases: 13/141 (9%)
- **Therapy for thyroid disease**
  - Antithyroid drugs only: 72/141 (51%)
  - Radioactive iodine: 42/141 (30%)
  - Thyroidectomy: 27/141 (19%)
- **Duration of thyroid disease in months (median and range)**
  - Since first symptoms: 22 (0–720)
  - Since diagnosis: 16 (0–700)

Table 3 Characteristics of the eye disease in 152 patients newly referred to EUGOGO centers because of Graves’ orbitopathy.

- **Duration in months (with range)**
  - Since first symptoms: 16 (1–720)
  - Since diagnosis: 12 (0–700)
  - No. of patients with unilateral eye involvement: 7/152 (5%)
  - No. of patients with positive von Graefe’s sign: 84/143 (59%)
  - Lid aperture (in mm) of most affected eye (mean±s.d.): 13.3±2.7
  - No. of patients with upper eye lid swelling: 113/144 (75%)
  - No. of patients with lower eye lid swelling: 98/144 (68%)
  - Proptosis of the most affected eye (mean±s.d.): 21.5±4.0 mm
  - No. of patients with Proptosis \( \geq 23 \) mm: 56/147 (38%)
  - No. of patients with diplopia: 71/145 (49%)
  - No. of patients with ocular torticollis: 10/144 (7%)
  - No. of patients with corneal involvement: 23/148 (16%)
  - No. of patients with Bell’s sign: 57/137 (42%)
  - No. of patients with lagophthalmos: 36/142 (25%)
  - No. of patients with optic nerve involvement: 29/149 (21%)
  - No. of patients with abnormal color vision: 9/145 (6%)
According to the clinical impression, 60% of the patients had active disease. When we compared these active patients with the patients thought to be inactive, the CAS was indeed higher in the active patients ($P < 0.001$; Fig. 1), and the active patients also had a shorter median duration of the eye disease: 12 months (range: 2–200) versus 34 (1–516); $P < 0.001$. However, a large overlap was found in both criteria (duration of the eye disease and the CAS) between the two groups. Imaging techniques for assessment of activity were not employed often: T2 relaxation times measured by MRI were performed in 18/152 (12%), octreotide scintigraphy was carried out in 18/152 (12%), and A-mode ultrasonography in 41/152 (27%) patients. CT-scans were, on the other hand, obtained in 102/152 (67%) patients, apparently to assess severity of the eye disease, MRI was performed in 28/152 (18%) patients. To assess the severity of the eye muscle involvement most centers used the Gorman score (performed in 95% of the patients).

The treatment plan as established after the complete evaluation of the patients (Table 4) appeared to be dictated by both the severity and the activity of the disease. In general, close review with or without local measures was planned in 38% of the patients, in 44% non-surgical therapy was planned (corticosteroids in 18%, radiotherapy in 4%, steroids combined with irradiation in 10%, and lanreotide/octreotide in 13%), whereas in the remaining 18% rehabilitative surgical measures were scheduled.

Using the overall clinical impression, non-surgical (immunosuppressive) treatment was planned in 66% of the patients with active disease, compared with only 9% of those with inactive disease, while rehabilitative surgery was more likely to be recommended in patients with inactive disease than in those deemed to be still active: 9% versus 33% (Chi-square 46.16; $P < 0.02$).

### Discussion

This first EUGOGO multi-center study has yielded some new data on the history of Graves’ orbitopathy patients. Only 33% of our orbitopathy patients had a positive family history for thyroid disorders, which appears to be lower than is usually seen in patients with Graves’ hyperthyroidism or Hashimoto’s disease (2). This may suggest that environmental factors may play a greater role in this specific manifestation of Graves’ disease. In this respect, it is surprising that only 40% of patients were current smokers. This may be due to the fact that many patients in our study only had mild eye disease, but a second explanation may be that the referring physicians have now started to advise their patients to stop smoking as the first step in their management.

The number of patients with euthyroid ophthalmopathy (3%) and with hypothyroidism as the presenting thyroid disorder (4%) are roughly in agreement with previous reports (13, 14).

As for the treatment of the hyperthyroidism, most centers used antithyroid drugs as the only way of managing the thyrotoxicosis (51%), which is in agreement with a survey of treatment practice in orbitopathy patients carried out in 1998 (15). Radioactive iodine was used much less often (in 30%), with the exception of the UK centers in which 55% of the patients had been treated with radioactive iodine.

It was striking to note that it took a long time (median 16 months since the onset of the eye symptoms) before the patients were actually seen by experienced physicians in orbital centers. In The Netherlands, Italy and the UK the patients were generally seen within 1 year, but in France and Greece the delay was over 2 years. In view of the markedly low quality

![Figure 1](https://www.eje.org)
of life, even in patients with only mild ophthalmopathy (1), this delay is inappropriately long, especially in view of the fact that the majority (68%) had not yet received any kind of treatment - not even eye drops - from the referring physician. This situation likely reflects the fact that the relative rarity of this disease precludes adequate measures being prescribed by general ophthalmologists or internists, and reinforces the view that more effort is warranted to promote early referral to specialized centers.

Most patients (40%) were assessed as having mild eye disease, but were still referred to specialized centers for further treatment. In agreement with recent data on their decreased quality of life, 26/59 (44%) were indeed offered specific treatment. The stage of the disease appeared to be important in determining further treatment. The majority (66%) of patients thought to have active eye disease qualified for immunosuppressive therapies, whereas rehabilitative surgery (if available) was mostly offered to patients with inactive disease. Assessment of disease activity was carried out according to local preferences, but correlated well with the CAS and the duration of the eye disease. Additional (expensive) imaging techniques like T2 relaxation time on MRI or octreotide scintigraphy, were carried out in a minority of patients.

Most patients (75%) had at least signs of soft tissue involvement, upper eye lid swelling being more frequent than lower eyelid involvement, whereas extraocular muscle involvement was present in half the patients. More severe signs such as keratopathy or optic nerve involvement were found in one-quarter of the patients. Only 51% of our patients were using local protective eye drops before referral, although many more patients were prone to develop keratitis, as assessed by the high prevalence of Bell’s phenomenon and of lagophthalmos. NOSPECS class 3 signs were found in only 38% of patients, reflecting the ill chosen cut-off of 23 mm. The upper limit of normal protrusion values in caucasians is 20 mm, and 63% of our patients had Hertel readings of ≥ 21 mm suggesting that the current NOSPECS classification underestimates the severity of this sign.

There were no great differences among the participating centers in the degree of severity or activity of the eye disease in this cohort of newly referred patients with Graves’ orbitopathy. It was reassuring to see that large numbers of patients with the three degrees of severity of the orbitopathy were gathered, including 42 patients with severe eye disease (due to the referral status of the EUGOGO centers). This finding is important, because it signifies that multi-center studies are possible in mild, moderate and severe orbitopathy. The current CRF needs to be refined in order to improve the compliance of the physicians, but indeed seems to be a feasible instrument to perform larger scale multi-center randomized clinical trials in the near future, which are necessary to improve management of this difficult disorder. The recruitment of 152 patients in only 4 months underscores the potential of the EUGOGO collaboration to set up such clinical trials.

References

1 Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF & Wiersinga WM. Quality of life in patients with Graves’ ophthalmopathy is markedly decreased: measurement by the Medical Outcomes Study instrument. Thyroid 1997 7 885–889.


