Assessment of disease activity in Graves' ophthalmopathy
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Assessment of disease activity in Graves’ ophthalmopathy by orbital ultrasonography

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References


Assessment of tissue activity in Graves' disease: implications for organ-specificity.

Abstract
In a previous, preliminary study we have found that A-mode ultrasonography might be useful in predicting the response to immunosuppression in Graves' ophthalmopathy. This suggested that a low internal reflectivity in the extraocular eye muscles reflects inflammatory changes, as compared to high and irregular reflectivity in fibrotic muscles. Thus, we performed a prospective study in 56 consecutive patients with moderately severe Graves' ophthalmopathy, who were treated with retrobulbar irradiation (10 fractions of 2 Gy). Before treatment the internal reflectivity was measured in the extraocular eye muscles, and then compared to the therapeutic outcome 26 weeks after irradiation. Twenty-eight (50%) of the patients responded favorably to radiotherapy, and when we used the reflectivity measured in the one eye muscle per patient which had the lowest reflectivity, the eye muscle echogenicity indeed tended to be lower in the responders than in the non-responders (P=0.09). From a receiver operator characteristics curve, a cut-off value of 30% yielded a good positive predictive value of 85%, but the negative predictive value was only 60%. In conclusion, this study confirms our preliminary findings that A-mode ultrasonography has a rather good positive predictive value. However, the poor negative predictive value precludes its use as sole activity parameter.

Introduction
Graves' ophthalmopathy (GO) is viewed as an autoimmune disease characterized by lymphocytic infiltration of the retrobulbar tissues. The infiltrating lymphocytes produce cytokines which stimulate glycosaminoglycan production by the orbital fibroblasts present in the extra-ocular eye-muscles (EOM) and the connective tissues, leading to edema and swelling of these tissues. In later stages, this inflammation subsides and is replaced by a fibrotic swelling of the eye muscles. Thus both the inflammatory and the fibrotic stage of the disease cause swelling of the retrobulbar tissues resulting in proptosis and diplopia. The
management of GO, however, differs during the active and the inactive phases: immunosuppression being more effective when there is inflammation, and decompressive or squint surgery being indicated during the fibrotic endstage.

It follows that the severity of the eye disease per se is not a good indicator for the choice between immunosuppression and surgery. Instead, one would want to know whether the disease is active or inactive. The gold standard for the determination of the activity of the eye disease is histological examination of retrobulbar tissues. An inflammatory reaction with lymphocytic infiltration in extra-ocular muscles and retrobulbar fat indicates active disease, whereas fibrotic changes in these tissues indicate inactive disease. Biopsies of retrobulbar tissues, however, are seldom feasible in clinical practice. In order to differentiate between these stages a number of various so-called disease-activity parameters have been introduced, including the Clinical Activity Score (CAS), Magnetic Resonance Imaging (MRI), and octreotide scanning. The CAS is a purely clinical and inexpensive measurement, but has a limited sensitivity and specificity. MRI and octreoscan have their own merit, but both are expensive and not available in all centers. We have previously reported on the use of A-Mode Ultrasonography. With this technique we found that patients with active disease had one or more eye muscles with very low internal reflectivity, presumably due to inflammation and edema leading to easy penetration of the sound beam. In contrast, patients with inactive and fibrotic disease had eye muscles with a high internal reflectivity, probably because of fibrosis in these muscles. A-Mode Ultrasonography is inexpensive and widely available method, and was found to be promising in our preliminary study in differentiating patients with active disease (in the absence of histology this was defined as those who had benefit of immunosuppression) from those with inactive disease (defined as those who did not respond to immunosuppressive radiotherapy).

Here we report on the usefulness of ultrasonography to predict the result of retrobulbar irradiation in a cohort of 56 patients with moderately-severe Graves' ophthalmopathy. It consisted of consecutive patients selected for radiotherapy
because of the severity of their eye disease, regardless of the "activity" of their disease, thus representing an average population of GO patients.

**Patients**

We studied consecutive patients with moderately severe GO, who had not been treated for their eye disease except for artificial tears. Moderately severe GO was defined by severe soft-tissue involvement, and/or proptosis of ≥25 mm, and/or an evident restriction in eye muscle motility, usually leading to diplopia. Patients with a decreased visual acuity due to optic nerve involvement were considered too severe, and not included in this study. All had to be euthyroid for at least 2 months, as indicated by the presence of normal plasma concentrations of thyroxine and tri-iodothyronine, in the absence of an elevated thyrotropin concentration. Patients with diabetes mellitus, previous chemotherapy or pregnancy were excluded from this study.

All patients were treated, (for reasons of moderate severity of their GO), with retrobulbar irradiation using 10 divided fractions of 2 Gy daily over a 2 week period administered with a 5 meV linear accelerator. Therapeutic outcome was assessed 26 weeks after irradiation and defined according to minor and major criteria. The major criteria were: 1) An improvement in the degree of diplopia, ranging from absent, to intermittent (i.e. present only occasionally), inconstant (i.e., present but not in primary gaze), or constant (i.e., present in primary gaze); 2) Improvement in the quantitative measurement of eye muscle motility by 8 degrees or more in elevation. Minor criteria were changes of ≥2 mm in lid width, ≥2 mm in exophthalmometer readings, and changes in soft-tissue involvement (i.e., mild, moderate or severe) as judged blindly from pre- and posttreatment colour slides. Patients who responded in at least one major, or in ≥2 minor criteria were considered responders. Patients in whom no changes occurred, or who responded in only one minor criterion, or who actually deteriorated classified as non-
responders. In addition, we also determined the pretreatment Clinical Activity Score.\textsuperscript{2}

The study protocol was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam, and all patients gave their informed consent for the study.

**Methods**

Eye muscle reflectivity was assessed by an experienced independent investigator with standardized A-mode ultrasonography of both orbits, using an Ophthascan-S unit (Alcon Co., Puurs, Belgium), as described earlier.\textsuperscript{6} In short, the sound beam was directed perpendicular to the axis of the rectus muscles, and reflectivity was determined at the muscle belly. From Polaroid pictures, taken during the examination, the eye muscle reflectivity was calculated by measuring the distance from the baseline to the mean of the tops of all spikes within the anterior and posterior muscle sheaths, and expressed as a percentage of the initial scleral spike, which was set at 100\% (Fig. 1). Due to the orbital rim it was difficult to obtain a reproducible image of the inferior rectus muscles. Therefore, we only assessed reflectivity in the superior, medial, and lateral rectus muscles. The intra-observer coefficient of repeatability is 10.2\%, and the inter-observer coefficient of repeatability is 11.9\% in patients with GO.\textsuperscript{6} To determine the predictive value, the therapeutic outcome was related to the mean pretreatment reflectivity in all six investigated eye muscles, and to the pretreatment reflectivity of the muscle with the lowest echogenecity.

**Statistical analysis**

All data are expressed as mean ± standard deviation and unpaired two-sided Student's t-tests were used. A receiver-operator-characteristics curve was plotted to determine the cut-off for the pretreatment lowest eye muscle reflectivity in
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predicting a response to treatment. Positive and negative predictive values were calculated from a 2x2 table using this cut-off.

Figure 1. Two examples of the A-mode ultrasonographic pattern of the orbital contents in a patient with inactive Graves' ophthalmopathy (A), and in a patient with active eye disease (B). Notice the irregular and high reflectivity pattern of the eye muscle (arrow, 69%) in patient A, and the low reflectivity (15%) in the eye muscle in patient B. Reflectivity was measured by determining the mean distance between the baseline and the tops of the spikes as a percentage of the initial scleral spike.

Results

Fifty-six patients (age 53.2 ± 10.5 yrs; 39 females, 17 males) were included in the study, of whom 28 (50%) responded to radiotherapy, whereas 50% did not respond. We compared the eye muscle reflectivity among the responders and non-responders (Table 1). There was no difference in eye muscle reflectivity when all eye muscles were considered together, however when we looked only at the eye muscle with lowest reflectivity per patient as described before, 6 responders tended to have a lower reflectivity than non-responders (P=0.09).
Table 1. Mean (SD) pretreatment Eye Muscle Reflectivity (EMR) in 56 patients with moderately-severe GO, of whom 28 responded and 28 did not respond to subsequent orbital radiotherapy. Lowest EMR represents the mean (SD) reflectivities in the one muscle with lowest reflectivity per patient.

<table>
<thead>
<tr>
<th></th>
<th>All n=112 eyes (56 patients)</th>
<th>Responders n=56 eyes (28 patients)</th>
<th>Non-responders n=56 eyes (28 patients)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>m. rectus superior</td>
<td>54 (8)</td>
<td>55 (9)</td>
<td>54 (7)</td>
<td>.54</td>
</tr>
<tr>
<td>m. rectus medialis</td>
<td>45 (11)</td>
<td>43 (11)</td>
<td>47 (10)</td>
<td>.16</td>
</tr>
<tr>
<td>m. rectus lateralis</td>
<td>49 (8)</td>
<td>47 (11)</td>
<td>51 (8)</td>
<td>.11</td>
</tr>
<tr>
<td>mean of six EMR (%)</td>
<td>n=56 patients</td>
<td>n=28 patients</td>
<td>n=28 patients</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>50 (6)</td>
<td>49 (7)</td>
<td>51 (6)</td>
<td></td>
</tr>
<tr>
<td>lowest EMR (%)</td>
<td>n=56 patients</td>
<td>n=28 patients</td>
<td>n=28 patients</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>36 (11)</td>
<td>33 (14)</td>
<td>38 (8)</td>
<td></td>
</tr>
</tbody>
</table>

For differences between responders and non-responders, unpaired independent two-sided t-tests were calculated (significance level p<0.05).

From a ROC curve (Fig. 2) we determined a cut-off of 30% reflectivity to be used to discriminate between responders and non-responders. A reflectivity of <30% in the eye muscle with lowest reflectivity, occurred more frequently in responders (11/28, 39%) than in non-responders (2/28, 7%; P=0.004). Using this cut-off, measuring eye muscle reflectivity had a good positive predictive value of 85% (Table 2). However, many responders had a reflectivity of ≥30% (Fig. 3), explaining the low negative predictive value of only 60%.
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Figure 2. Curve of receiver operating characteristics at different cut off points of the lowest eye muscle reflectivity (expressed as a percentage), predicting a response to immunosuppressive treatment. The area under the curve is 0.61. A cut-off of 30% reflectivity yielded the best discriminating value (arrow).

Table 2. Two-by-two table showing the usefulness of A-mode ultrasonography in predicting a response to immunosuppressive treatment. A cut off of 30% for the lowest eye muscle reflectivity in a patient was calculated from a receiver operating characteristics curve at different cut off points of lowest eye muscle reflectivity.

<table>
<thead>
<tr>
<th>lowest EMR (%)</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>totals</th>
<th>predictive values</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>11</td>
<td>2</td>
<td>13</td>
<td>+PV=85%</td>
</tr>
<tr>
<td>≥30%</td>
<td>17</td>
<td>26</td>
<td>43</td>
<td>-PV=60%</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>28</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Fischer's exact test, two tailed: p=0.004.
No correlation could be found between the Clinical Activity Score and eye muscle reflectivity. Actually, out of 13 patients with a low CAS of 0-1, 5 had a reflectivity of less than 30%. This indicates that A-mode ultrasound measures an activity feature different from the signs and symptoms considered in the CAS.

**Discussion**

In our first preliminary study we found that the measurement of EOM reflectivity by ultrasound was a reliable and inexpensive method with a promising capacity to differentiate patients who will respond to immunosuppressive
treatment from the non-responding patients. Here we tested this non-invasive method in a large group of 56 consecutive patients with moderately-severe GO, not selected for disease activity, who underwent retrobulbar irradiation. The treatment resulted in a response in 28 patients (50%), and our A-mode ultrasonography could identify 11/28 (39%) of these responders by detecting at least one eye muscle with <30% reflectivity. In only 2/28 (7%) non-responders such a low reflective eye muscle could be found. Therefore, this method proved to have a good positive predictive value of 85%.

On the other hand, this large study also revealed a poor negative predictive value (60%), because 15/28 patients responding to radiotherapy did not have a low reflective eye muscle. This is in contrast to our earlier study in which a negative predictive value of 100% was found, though with a wide 95% Confidence Interval of 45-100%. Our present results thus underscore the need to confirm our previous preliminary results in a larger prospective study. One reason for the disappointingly low negative predictive value probably is the fact that the ultrasound beam can not reliably assess the inferior rectus muscle (due to obstruction by the superior orbital rim). This inferior rectus is the most frequently involved eye muscle in GO, and it might very well be that many of the responders actually had a low reflectivity in their inferior recti, which is missed by our method. For, in most patients only one or two eye muscles had low reflectivity with normal values in the other muscles. This is in agreement with our first study, and with the fact that the eye muscles in GO are usually differentially affected.

So, what might be the role of A-mode ultrasonography in assessing disease activity in GO? Its rather poor negative predictive value precludes its use as sole activity parameter and it should thus be combined with other methods. In this respect it is interesting to note that ultrasound reflectivity did not correlate with the Clinical Activity Score. It seems that ultrasound identifies a subset of patients responding to radiotherapy, who do not have a high CAS; ultrasonography therefore appears to assess a different activity feature. It could be that ultrasonography measures eye muscle information, whereas the CAS reflects
activity in all of the orbital tissues. Other methods that assess the activity of GO are Magnetic Resonance Imaging (MRI) and octreotide scintigraphy. However, these methods are expensive and not always available. Therefore, ultrasonography (being inexpensive, noninvasive, and safe)\(^1\) might very well be useful in identifying active patients in conjunction with other methods. Its true place can only be established in a study in which all available methods are applied in the same patient population.

In conclusion, A-mode ultrasonography can identify a relatively small number of patients responding to radiotherapy, who are nevertheless not identified by other simple clinical means such as the Clinical Activity Score. However, if no low reflective eye muscles are detected, this does not mean that a patient will not benefit from radiotherapy.

**Acknowledgement**

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**References**


