Title:

Raising Awareness of Graves’ Orbitopathy with Early Warning Cards

Short running title:

Graves’ Orbitopathy Early Warning Cards

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Key words:

Graves’ disease, Graves’ hyperthyroidism, Graves’ orbitopathy, thyroid eye disease
Abstract:

Background: Clinically significant Graves’ orbitopathy (GO) develops in about 25% of those with Graves’ disease (GD); most cases of GD in the UK are managed by endocrinologists. Despite this, patients report significant delays before a diagnosis of GO is made. Measures to increase awareness of the early signs of GO and establishing a fast-track referral pathway to specialist care should overcome these delays and potentially improve outcomes.

Aims: We aimed to determine whether issuing a “GO early warning card” to all GD patients raises awareness of GO and facilitates early diagnosis, what percentage of cards result in a telephone contact, the number of “false reports” from card carriers and patient perceptions of the cards.

Methods: We designed cards, detailing common GO symptoms and a telephone number for patients developing symptoms. Cards were distributed to 160 GD patients, without known GO, attending four endocrine clinics in the UK (December 2015 - March 2016). We recorded telephone contacts over twelve months from when the last card was distributed and gathered patient feedback.

Results: The early warning cards were well received by patients in general. Over twelve months, ten telephone contacts from nine patients, all related to ocular symptoms, were received (6% of cards issued). Nine calls resulted in an additional clinic review (for eight patients) and four diagnoses of GO were made.

Conclusions: This pilot study demonstrates that it is feasible to distribute GO early warning cards in clinic and that they can be used to facilitate an early diagnosis of GO.
Background:

Graves’ orbitopathy (GO) is an orbital inflammatory condition associated with circulating anti-TSH receptor antibodies (TRAb). Clinically significant GO is present in about 25% of those diagnosed with Graves’ disease (GD) and, in the majority of cases, develops following thyroid dysfunction. Over an 18 month period, of those with GD without GO at baseline, approximately 13% can be expected to develop GO. In the most severe cases, GO can be sight-threatening. However, even mild GO can cause significant ocular symptoms which can have a negative impact upon quality of life. At any one time, there is a group of patients with GD attending endocrine clinics with subtle symptoms and signs of GO which are easily overlooked. A number of inexpensive interventions have been demonstrated to be safe and effective in the management of individuals with mild active GO, making early identification of cases worthwhile. These include selenium supplements, which have been shown to prevent progression of mild active GO and improve quality of life. In addition, topical lubricants in the form of eye drops and ointments are effective means of preventing corneal ulceration. Finally, smoking is associated with increased incidence and greater severity of GO and smoking cessation has been shown to correlate with better response to medical treatments.

As the early manifestations of GO are easily confused with other more common eye conditions such as infective or allergic conjunctivitis, and most primary care physicians are unfamiliar with the early manifestations of GO which can result in subtle ocular symptoms and signs that can be easily overlooked, diagnostic delays are unfortunately common. These are a significant source of patient dissatisfaction and result in delays in treatment and increased morbidity. The Amsterdam Declaration, signed by professional and patient-led organisations, pledged to address this issue, aiming to reduce time to GO diagnosis by 50% - a challenging target if the patient and their primary care physician are unaware of the condition. TEAMeD (The Thyroid Eye Disease Amsterdam Declaration Implementation Group UK; http://www.btf-thyroid.org/projects/teamed) was established to implement this declaration in the UK. We argued that since 90% of cases of GO are reported to occur either concomitant with, or after, the diagnosis of hyperthyroid or hypothyroid GD, and the majority of patients with GD in the UK are under the care of an endocrinologist, by making all patients with a confirmed diagnosis of GD aware that they are at risk of GO (and how to reduce the risk), we might both reduce the incidence and the time to presentation of the disease. Since GO can present up to three years or more after the diagnosis of GD, the aim was to provide information on the early signs of GO in a form which would be retained in an easily accessible way by patients. We therefore devised a wallet-sized “GO early warning card” describing the key symptoms of GO and preventive measures, as well as a named telephone contact and an internet
The intention was that the cards would alert patients to early relevant symptoms and, by using the contact number, avoid referral delays. However, since some of the early symptoms are relatively non-specific, the concern was that distributing the cards to all patients with GD would generate patient anxiety and large numbers of inappropriate self-referrals. Here we report a four centre study to evaluate the performance of such an “early warning card” system.

**Methods:**

We designed credit-card sized GO early warning cards (figure 1), which have a list of the common symptoms of GO that patients can recognise themselves, chosen by consensus opinion from the Vancouver Orbitopathy Rule study\(^1\), and a local contact telephone number for patients who develop eye symptoms. We aimed to distribute a minimum of 150 cards (predicting that a maximum of 20 individuals, 13%, could be expected to develop clinically significant GO over an 18 month period and therefore 13 could be expected to develop GO over a twelve month period\(^1\)). In total, cards were distributed to 160 consecutive patients with GD (defined as those with hyperthyroidism/subclinical hyperthyroidism and smooth, symmetrical goitre or positive TSH receptor antibodies (TRAb) or diffuse uptake on thyroid radionuclide scan) in endocrinology clinics between December 2014 and March 2015, with instructions to read the cards, note that there was a local contact number and to keep the card in an accessible place (e.g. a wallet) for future reference. No restriction was placed on the duration of Graves’ disease, with cards being given to new and follow-up patients. Patients with relapsed GD were also included however individuals already known to have GO were excluded. The cards had a serial number which could be matched to each patient and patients were asked to provide an email or postal address for feedback. The study was conducted across four UK endocrine clinics (Newcastle, Exeter, Cardiff and Edinburgh). In the following twelve months, we documented any telephone contact made as a consequence, and the outcome of these calls. After 12 months, we reviewed the last clinical letter of all card recipients to determine whether any had developed GO but had not reported this via telephone helpline. In June 2016, three months after the last card was distributed, we asked patients for feedback, by email or post, about the scheme. Feedback was sought via an online or postal questionnaire comprising 9 questions (table 1). A single email reminder was sent 2 months following the initial feedback request. For individuals without access to email, the same survey was sent out by post with a stamped-addressed return envelope.

**Results:**
One hundred and sixty cards were distributed in total. The age range of card recipients was 18 to 84 years (median age 47 years) and 123/160 (77%) card recipients were female. The median number of years since GD diagnosis for all card recipients was 2 years (range 0 to 30 years). 37/160 (23%) had had one or more relapses (table 2).

Over twelve months, ten telephone calls from nine patients were received (one patient called twice), therefore 6% of cards distributed resulted in telephone contact (figure 2). Nine of the ten calls received occurred within the first three months of the follow-up period. All ten calls related directly to ocular symptoms. One call was managed with telephone advice alone. In this case, the individual had symptoms classical of transient ischaemic attack and was advised to see their GP for further assessment. One call was initially managed with telephone advice, however following a second call from the same individual, a clinic review was arranged. The other seven calls resulted in an additional clinic review. Of the eight patients offered clinic review, six were initially seen in an endocrinology clinic at a tertiary referral centre by a consultant or specialist registrar and two were seen directly in a multidisciplinary thyroid-eye clinic. Two of the six patients reviewed initially in an endocrinology clinic had a diagnosis of mild, active GO and were offered further review in a specialist multidisciplinary thyroid-eye clinic. Of the two patients seen directly in the multidisciplinary thyroid-eye clinic, one was found to have mild active GO and the other was found to have mild inactive GO. All three individuals confirmed to have active GO were offered smoking cessation advice if relevant, topical treatment and/or selenium supplements. Therefore, in total, four diagnoses of GO were made (table 3). After the initial clinical review and initiation of treatment, all four patients were followed up: symptoms and signs of GO had fully resolved in 3/4 when followed up between 2 and 6 months following presentation, and significantly improved in 1/4 at 2 months’ follow up. The sensitivity of the early warning cards can be calculated at 44% (given that nine individuals telephoned, one received a diagnosis of TIA and was directed to the appropriate services, eight were reviewed in clinic and four of these had GO).

At twelve months, clinical letters for all warning card recipients were reviewed to determine what proportion had developed clinically significant GO during the follow-up period but had not reported it via the telephone helpline. In total, of the 160 individuals who had received a card, 5 had developed GO within the twelve month follow-up period but had not called the helpline (figure 2). Three individuals were noted to have minor ophthalmic abnormalities (periorbital swelling, eyelid redness, eyelid swelling) during routine endocrinology follow-up appointments at 10, 8 and 6 months following receiving an early warning card, but were asymptomatic. Two individuals had developed symptoms of GO but had not telephoned to report these. 1 presented to their GP with
eyelid swelling 3 months after receiving a warning card and was referred to the local joint thyroid eye clinic. The other complained of a change in the appearance of their eyes 8 months following receiving a warning card when attending their routine endocrinology outpatient follow up and was referred to the local joint thyroid eye clinic. Both were diagnosed with mild, active GO. As 5 of the 151 individuals who had not called the telephone helpline in the twelve month follow-up period were found to have developed GO on review of clinic letters, the specificity of the early warning cards can be calculated as 97%.

After three months, all card recipients were asked for feedback via email or postal survey. Forty-nine of the 160 participants (31%) responded (figure 2). Of these 49 people, 45 remembered receiving a card; 40/45 participants (89%) thought that it had been useful to receive the early warning card and 44/45 (98%) stated that they had clearly understood what the purpose of the card was. It was reported by 24/45 (53%) that they kept their card at home, while 21/45 (47%) reported keeping it on their person e.g. in their wallet.

Of the 45 responders who remembered receiving a card, eight (18%) reported that they had had eye problems of some description since receiving the card however only three (7%) had called the telephone number on the card during the three-month observation period before feedback was sought. Of these, one had found the telephone consultation very helpful, one reported that it was somewhat helpful and one reported that it was not helpful as they had been unable to speak to anyone. To determine whether participants kept the cards, survey responders were asked to quote their card’s unique serial number at the end of the survey and 30/45 participants (67%) were able to do so, suggesting that most participants retained their card.

**Discussion:**

We have found that it is practical to distribute GO early warning cards to patients in busy endocrinology clinics. Some of the endocrinology clinicians participating in the study reported that the cards acted as a prompt to discuss GO symptoms and possible prevention measures with individuals with GD. In the cohort studied, the GO early warning cards do not result in an excessive number of telephone calls and all calls that were received were related to ocular symptoms and were therefore appropriate. The cards were appreciated by the majority of patients from whom feedback was received. Three individuals who had contacted the telephone helpline responded to the request for feedback and one reported that they had been unable to contact someone for advice and was therefore dissatisfied. If this scheme were to be rolled out more widely, the logistics of providing a
telephone helpline service would need to be clarified. For example, the card would need to stipulate when individuals could expect to speak to someone, perhaps using an answer machine service to ensure that patient expectations were met.

The majority of the telephone enquiries that were received resulted in an additional clinic review (for 8 individuals in total; 5% of those receiving a card). Depending upon the local service structure, patients were reviewed either in a specialist endocrinology clinic, by an endocrinologist, or in a multidisciplinary thyroid-eye clinic. In total, 1/8 had inactive GO and 3/8 had active disease and were offered treatment. At subsequent follow-up, signs and symptoms of GO had significantly improved in 1/4 and entirely resolved in 3/4 patients, suggesting that GO is often transient, as noted by others\textsuperscript{1}. Therefore, the sensitivity of the early warning cards can be calculated at 44% (given that nine individuals telephoned, one received a diagnosis of TIA and was directed to the appropriate services, eight were reviewed in clinic and four of these had GO). Of the 151 individuals who had not called the telephone helpline in the twelve month follow-up period, review of the clinic letters revealed that 5 had since developed signs and/or symptoms of GO therefore the specificity of the early warning cards can be calculated as 97%.

An ongoing study looking at the incidence of GO in individuals with recently diagnosed GD (excluding those with GO at the time of presentation with GD) has found that, over a 12 month period, 16% of individuals will develop GO (with 2% developing moderate-to-severe disease) (W. Wiersinga, personal communication, 18/4/17). In our study, this equates to 26 participants predicted to develop GO, with three of these predicted to develop moderate-to-severe GO. Tanda \textit{et al}\textsuperscript{1} followed-up a large cohort of individuals with newly diagnosed GD without GO at baseline and found that, at 18 months, approximately 13% had GO, with the majority of cases being mild. In our study, this equates to 13 individuals predicted to develop GO over 12 months. In total, we observed that 9 people developed GO over 12 months (all cases were mild) and the early warning card scheme captured 4/9 cases. The total number of cases in the cohort is less than expected, and this is likely due to the fact that a significant proportion of the cohort were follow-up patients, with a range in years from diagnosis of 0 to 30 years (median 2 years) or patients with a relapse of GD rather than newly diagnosed individuals. Including a greater number of participants at the outset of the study, or including only individuals with newly or recently diagnosed GD, would likely have resulted in a greater number of cases of GO being identified. It is also possible that if only those with newly or recently diagnosed GD were given early warning cards, that the number of telephone calls to the helpline would increase as a result of increased incidence of GO in these individuals as compared with follow-up cases. Another factor which might increase telephone contacts if this
group was studied exclusively is that they have had fewer patient-physician consultations compared to follow-up patients, and therefore might have more questions or concerns regarding minor ocular symptoms compared to patients who have been under clinic follow-up for longer.

The early warning card scheme enabled 4/160 patients with Graves’ disease (3%) to receive an earlier diagnosis of GO, however an additional 5 patients developed symptoms or signs of mild GO during the follow-up period but did not report these through the telephone helpline. Three of these 5 individuals were asymptomatic and noted to have minor ophthalmic abnormalities during routine endocrine follow-up appointments which explains why they did not call the helpline. Two individuals however had developed symptoms of GO but had not telephoned to report these. Possible reasons for this include patient preference not to draw attention to their symptoms, mild symptoms not troublesome or worrying to the patient or having a follow-up appointment already scheduled meaning they would be able to report their symptoms early without the need for additional support. In addition, as the majority of telephone calls resulting from the early warning cards were made early on (within 3 months of the cards being distributed), it is possible that the patients who developed GO but not used the helpline had forgotten about the warning cards (30/45 card recipients (67%) who responded to the request for feedback were able to correctly report the serial number on the card after 3 months confirming it was still in their possession) and that the intervention offered only short-term benefit without reinforcement. Further studies will be required to elucidate the underlying reasons.

The value of early detection of mild, often transient, GO can be questioned given that all cases of GO detected in the cohort studied were mild with the majority of cases resolving at subsequent follow-up. However, we argue that early detection is worthwhile as simple interventions such as ensuring biochemical euthyroidism, selenium supplements, topical lubricants and smoking cessation advice may have averted progression of the eye disease. Furthermore, the use of such cards ensures that effective preventive measures for GO (smoking, euthyroidism, careful use of radioactive iodine treatment) are considered and discussed in all patients with GD, when currently these may be overlooked. In addition to offering a card to all patients with GD at diagnosis, it would be worthwhile reinforcing the message, and offering a new card if appropriate, in those clinical circumstances when the risk of new-onset of GO or exacerbation of GO is increased, for example at the time of radioiodine therapy. In this instance, GO early warning cards would serve to highlight the risks to the patient and encourage them to report any new ocular symptoms.
Medical treatments for GO (such as steroids\textsuperscript{16}, rituximab\textsuperscript{17}, teprotumumab\textsuperscript{18}) are most effective when administered early in the course of the disease, between 6-9 months from the onset of symptoms. However, a recent UK-based study showed that the average time that it takes for patients to receive a diagnosis of GO from their first visit to any doctor with symptoms of GO is 9.37 months\textsuperscript{19}. Many patients therefore currently miss the window for best response to medical therapies, because the diagnosis of GO is made too late.

The incidence of GO seems to be falling, and this is likely, in part, due to better endocrine care and increased awareness of prevention and early detection of GO. In addition, studies of the natural history of GO have demonstrated that if moderate-to-severe GO is going to develop, this occurs rapidly, in weeks rather than months, and therefore in order to prevent progression, early diagnosis and treatment is required. Immediate referral to ophthalmology is probably unnecessary in clinical practice, as the assessments can be performed by appropriately trained endocrinologists or endocrine specialist nurses and simple treatments that have virtually no side-effects can be initiated in the endocrine clinic setting. The cost of printing early warning cards is minimal at €0.32 (£0.28) per card. In total, 11 additional clinic appointments (7 follow-up endocrinology outpatient appointments costing €107 (£93) per appointment; 4 new patient ophthalmology outpatient appointments costing €122 (£106) per appointment\textsuperscript{20}) were made as a consequence of the study, resulting in a total cost of €1242 (£1075) (€ 311; £269 per single diagnosis of GO made). It has been estimated that the direct cost of moderate-to-severe GO is €373 (£317) per patient per annum, while indirect costs, due to sick leave, disability etc are between €3301-€6683 (£2808-£5685) per patient per annum\textsuperscript{21} therefore early detection and treatment, which may prevent progression to moderate-severe disease appear worthwhile. If awareness and prevention strategies are instituted nationwide, and appropriate simple measures are instituted early for GO that does develop, it may be possible to make a major impact on both the incidence of GO, and in particular the severity of occurrences of GO, with resultant major reduction in the morbidity of the disease, as demanded by the Amsterdam Declaration.

**Conclusion:**

GO early warning cards can be used to alert both patients with GD and the physicians caring for these individuals to the risk of GO and are well received by patients. They do not result in an excess burden of telephone contacts and resulted in early detection of GO in 45\% of cases. Regular reinforcement of risk awareness may result in more cases being detected early. GO early warning cards can be successfully used to fast-track patients with GD who develop ocular symptoms to
receive an earlier specialist assessment for GO and potentially an earlier diagnosis and treatment, and represent a simple and cost-effective intervention.

References:

7. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. Thyroid. 2010; 20:777-83


Table 1: Questions included in the GO Early Warning card patient perceptions survey

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you remember receiving a Thyroid Eye Disease Early Warning Card?</td>
</tr>
<tr>
<td>2. If you do remember receiving a card, where did you keep it?</td>
</tr>
<tr>
<td>3. Was it clear to you what the card was for?</td>
</tr>
<tr>
<td>4. Do you think that it has been helpful to have a card about thyroid eye disease?</td>
</tr>
<tr>
<td>5. Since you received the card, have you had any problems with your eyes that you believe were</td>
</tr>
</tbody>
</table>
due to thyroid eye disease?

6. Since you received the card, have you used the helpline number?

7. If you did call the helpline, did you find the advice that you received helpful?

8. Please enter the serial number of your thyroid eye disease warning card below

9. If you have any other comments about this initiative, please enter them below.

Table 2: Demographic details of GO early warning card recipients at each participating centre

<table>
<thead>
<tr>
<th>Centre</th>
<th>Age range (median age)</th>
<th>Number of female:male recipients</th>
<th>Basis of diagnosis</th>
<th>Duration of GO in years (median duration)</th>
<th>Number of relapsers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ TRAb</td>
<td>Diffuse uptake</td>
<td></td>
</tr>
<tr>
<td>Exeter</td>
<td>18-84 (48)</td>
<td>59:18</td>
<td>64/77</td>
<td>11/77</td>
<td>0 – 15 (2)</td>
</tr>
<tr>
<td>Newcastle</td>
<td>18-78 (41)</td>
<td>32:12</td>
<td>40/44</td>
<td>3/44</td>
<td>0 – 11 (1)</td>
</tr>
<tr>
<td>Cardiff</td>
<td>14-70 (50)</td>
<td>18:3</td>
<td>20/21</td>
<td>0/21</td>
<td>0 – 18 (2)</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>23-71 (40)</td>
<td>14:4</td>
<td>17/18</td>
<td>1/18</td>
<td>0 – 29 (3)</td>
</tr>
</tbody>
</table>
Table 3: Characteristics of the 4 individuals who had a diagnosis of GO made following clinical review, initiated after using the GO Early Warning card.

<table>
<thead>
<tr>
<th>Age, sex</th>
<th>Year of GD diagnosis</th>
<th>Smoker?</th>
<th>Symptoms</th>
<th>Action taken following contact (interval between contact and review)</th>
<th>Findings on initial clinical review</th>
<th>Diagnosis</th>
<th>Treatment initiated</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 F</td>
<td>2015</td>
<td>Yes</td>
<td>Eye discomfort and dryness</td>
<td>Endocrine OP clinic appointment made (1 day)</td>
<td>Mild proptosis on the left</td>
<td>Mild active GO</td>
<td>Smoking cessation advice</td>
<td>Offered 1 month review TED OP clinic (patient did not attend). Seen in TED OP clinic at 2 months</td>
<td>Symptoms improved, occasional grittiness and mild eyelid swelling in the morning. Discharged with further smoking cessation advice and topical lubricants</td>
</tr>
<tr>
<td>46 F</td>
<td>1999</td>
<td>No</td>
<td>Peri-orbital puffiness and “staring” eyes</td>
<td>Selenium, topical lubricants, TFT checked. TED OP clinic appointment made after further patient phone contact (4 days after 2nd contact, 21 days after 1st contact)</td>
<td>CAS 1/10; NO SPECS 2</td>
<td>Mild inactive GO</td>
<td>Selenium, topical lubricants</td>
<td>2 month review TED OP clinic</td>
<td>All signs and symptoms resolved. Discharged.</td>
</tr>
<tr>
<td>55 F</td>
<td>2015</td>
<td>Yes</td>
<td>Surface symptoms, orbital pain on upward gaze, change in appearance</td>
<td>TED OP clinic appointment made (28 days)</td>
<td>CAS 4/7; NO SPECS 2, minor proptosis on the right</td>
<td>Mild active GO</td>
<td>Selenium, topical lubricants, smoking cessation advice</td>
<td>6 month review TED OP clinic</td>
<td>All signs resolved. Occasional residual mild orbital pain on upwards gaze. Discharged, smoking cessation advice reiterated</td>
</tr>
<tr>
<td>52 F</td>
<td>2015</td>
<td>No</td>
<td>Eye pain, watering and horizontal diplopia</td>
<td>Endocrine OP clinic appointment made (14 days)</td>
<td>CAS 1/7; minor proptosis</td>
<td>Mild active GO</td>
<td>Selenium, topical lubricants</td>
<td>6 month review TED OP clinic</td>
<td>All signs and symptoms resolved. Discharged.</td>
</tr>
</tbody>
</table>

Key: GO – Graves’ orbitopathy; GD – Graves’ disease; OP – outpatient; TFT – thyroid function tests; TED clinic – multidisciplinary joint thyroid-eye disease clinic
Figure Legends:

**Figure 1:** GO Early Warning card. Panel A – back cover; Panel B – front cover; Panels C and D – inner text

**Figure 2:** Flowchart of GO early warning card study results