

Does Graves' Orbitopathy Ever Disappear? Answers to an Old Question

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Keywords

Graves' orbitopathy · Graves' disease · Thyroid · Autoimmunity

Abstract

Objectives: There is a general belief that Graves' orbitopathy (GO) is a "chronic" disease, namely that patients' eyes do not return to how they were before GO appeared. Here, we investigate this issue from both the patient's and the physician's point of view. **Study Design:** We studied the disappearance of GO, regardless of treatment, in all consecutive patients with a GO history of at least 10 years who came for a follow-up visit over a period of 5 years. Patients underwent an ophthalmological examination and were asked to answer a questionnaire on self-perception related to GO. **Results:** We studied 99 consecutive patients with a GO duration ≥ 10 years. Between the first and the last observation, patients received several types of treatment for their thyroid disease and/or for GO. At the end of follow-up, GO was considered disappeared based on objective criteria in 8 patients (~8%) and based on subjective criteria in 24 patients (~24%). When we considered both subjective and objective criteria, only 2 patients (~2%) had all criteria fulfilled and could be consid-

ered as GO-free. **Conclusions:** GO is a chronic disease in the vast majority of patients. Even after a very long time since its onset, complete disappearance is rare, although a minority of patients believe they do not have GO anymore and an even lower proportion do not have relevant GO signs. Our findings have obvious implications in patient management and counseling.

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Introduction

Graves' orbitopathy (GO) is a disfiguring and disabling disease that profoundly impairs the quality of life of affected patients [1–4]. The natural history of GO is characterized by an initial phase in which signs and symptoms worsen rapidly, up to a peak of maximum severity, then improves and finally reaches a static plateau, however without resolving to a normal condition [5–13]. Thus, there is a general belief among physicians involved with GO that this syndrome is somehow "chronic," namely that the patient's eyes do not return to how they were before GO appeared [1–13]. The ideal way to assess whether this is actually the case would be to objectively

examine patients before the occurrence of GO and then after a long follow-up period. Obviously, this is not possible, which leaves room only for two ways of answering the question, namely evaluation of GO signs based on accurate ophthalmological evaluation and patient self-assessment, with all the due biases that the former approaches carry. Thus, even with a long follow-up time, evaluation by physicians can be hampered by a series of confounding factors on what the definition of a normal eye is. For example, a normal eye protrusion range is somehow established [14–18], but patients may have constitutional or myopic exophthalmos that may not be distinguishable from GO exophthalmos. The issue of GO disappearance was investigated in two previous studies, but none of them considered disappearance of GO from both the clinician's and the patient's points of view [19, 20]. In an attempt of answering the question of whether GO disappears and to what extent it does so, we designed a perspective study in which both the objective point of view of the clinician and the subjective point of view of the patient were considered. Our results suggest that GO is in fact a chronic disease that disappears only in a minority of patients, regardless of thyroid and eye treatments.

Subjects and Methods

Study Design

In this study, we investigate the disappearance of GO, regardless of treatment, in all consecutive patients with a history of GO of at least 10 years who came for a follow-up visit in our GO clinic over a period of 5 years.

Study Registration and Approval

The study was registered at ClinicalTrials.gov (registration number: NCT03103607). Being an observational study, approval by the local review board was not required. Informed consent was obtained from all patients.

Patients

A total of 99 consecutive patients seen in our GO Clinic between 2010 and 2014 were enrolled. All patients underwent an ophthalmological examination, which included: (i) exophthalmometry; (ii) evaluation of the clinical activity score (CAS) according to Mourits et al. [21]; (iii) assessment of diplopia, which was classified according to the Gorman score [3] into absent, intermittent, inconstant, and constant; (iv) measurement of visual acuity; (v) assessment of the corneal status; and (vi) examination of the fundi. Patients were asked to answer a questionnaire on self-perception related to GO with the following questions: (i) "Are your eyes identical to the way they were before GO appeared?"; (ii) "Are your eyes normal?"; (iii) "Do you have any limitations in daily activities related to your eyes?"; and (iv) "Do you have any limitations in social life related to your eyes?".

Table 1. Demographic and clinical features of 99 patients with long-standing (≥ 10 years) GO

Age, years (range)	58.6 \pm 11.0 (30–84)
Gender	
Male	30
Female	69
Smoking habits	
Nonsmokers	34
Ex-smokers	33
Current smokers	32
GO duration, months	177 (148–219)
Thyroid disease	
Graves' hyperthyroidism	97
Hypothyroid autoimmune thyroiditis	2
Thyroid treatment	
Radioiodine and then LT ₄	64
Thyroidectomy and then LT ₄	23
Total thyroid ablation	10
LT ₄ for primary hypothyroidism	2
GO treatment	
ivGC (<i>n</i> = 56)	10 ivGC alone, 20 OR, 5 OR+OD, 5 OR+OD+MS, 1 OR+OD+PS, 4 OR+MS, 4 OR+PS, 5 OD, 1 OD+MS, 2 MS
oGC (<i>n</i> = 25)	17 oGC alone, 2 OR; 1 OR+OD+PS, 5 OD
OR (<i>n</i> = 41)	20 ivGC, 5 ivGC+OD, 5 ivGC+OD+MS, 4 ivGC+MS, 3 ivGC+PS, 1 ivGC+OD+PS, 2 oGC; 1 oGC+OD+PS
OD (<i>n</i> = 27)	6 OD alone, 5 ivGC, 5 ivGC+OR, 5 ivGC+OR+MS, 1 ivGC+OR+PS, 1 ivGC+MS, 2 oGC; 1 oGC+OR+PS
MS (<i>n</i> = 12)	2 ivGC; 4 ivGC+OR, 5 ivGC+OR+OD, 1 ivGC+OD
PS (<i>n</i> = 6)	1 PS alone; 3 ivGC+OR, 1 ivGC+OR+OD, 1 oGC+OR+OD
Untreated	11

Numerical values are reported as mean \pm SD (age) or median and IQR (GO duration) as appropriate. GO, Graves' orbitopathy; ivGC, intravenous glucocorticoids; OR, orbital radiotherapy; OD, orbital decompression; MS, muscle surgery; PS, palpebral surgery; oGC, oral glucocorticoids.

Outcome Measures

The primary outcome was the disappearance of GO at the last visit, namely the absence of objective signs, of subjective symptoms, and of any limitations in daily and social activities related to

Table 2. Features of GO**a** Features of GO in 99 patients with long-standing (≥ 10 years) eye disease at the first and last observation

	First observation	Last observation	<i>p</i> value
Exophthalmometry (most prominent eye), mm	21.5 \pm 3.3 (13–30)	19.7 \pm 2.7 (13–27)	<0.0001
Clinical activity score, mm	2.7 \pm 1.4 (0–6)	0.9 \pm 1.0 (0–4)	<0.0001
Diplopia, <i>n</i> (%)			
Absent	57 (57.5)	63 (63.6)	ns
Intermittent	12 (12.1)	4 (4.4)	
Inconstant	20 (20.2)	27 (27.2)	
Constant	10 (10.1)	5 (5.0)	
Visual acuity (decimals), mm	9.4 \pm 1.9 (1–10)	9.5 \pm 1.4 (3–10)	ns

Numerical values are reported as mean \pm SD with ranges in parentheses. GO, Graves' orbitopathy; ns, nonsignificant.

b Features of GO in 37 patients seen for the first time in the same period as patients in **a**, but lost to follow-up

	First observation	<i>p</i> value (vs. patients in a)
Exophthalmometry (most prominent eye), mm	20.4 \pm 3.3 (14–26)	ns
Clinical activity score, mm	2.8 \pm 1.4 (0–5)	ns
Diplopia, <i>n</i> (%)		
Absent	14 (37.8)	ns
Intermittent	9 (24.3)	
Inconstant	10 (27.0)	
Constant	4 (10.8)	
Visual acuity (decimals), mm	9.6 \pm 1.8 (1–10)	ns

Numerical values are reported as mean \pm SD with ranges in parentheses. GO, Graves' orbitopathy; ns, nonsignificant. *p* values were obtained by paired *t* test, except for diplopia (χ^2 test).

GO. The secondary outcomes were (i) the disappearance of GO at the last visit based on objective criteria, namely the absence of any signs of GO; and (ii) the disappearance of GO at the last visit based on subjective criteria, namely the absence of symptoms and of any limitations in daily and social activities related to GO.

GO was considered disappeared when the following criteria were fulfilled: objective criteria: (i) exophthalmos ≤ 19 mm in men and ≤ 17 mm in women; (ii) CAS $\leq 1/7$ points; (iii) absence of diplopia; (iv) normal visual acuity, or reduction of visual acuity unrelated to GO; (v) normal corneal status; and (vi) no GO-related alterations of the fundi; subjective criteria (questionnaire): (i) perception of both eyes identical to the way they were before GO appeared; (ii) perception of both eyes as normal; (iii) no eye-related limitations in daily activities; and (iv) no eye-related limitations in social life.

Statistics

Comparisons of categorical variables were performed by the χ^2 test. Comparisons of numerical variables were performed by unpaired or paired *t* test, as appropriate.

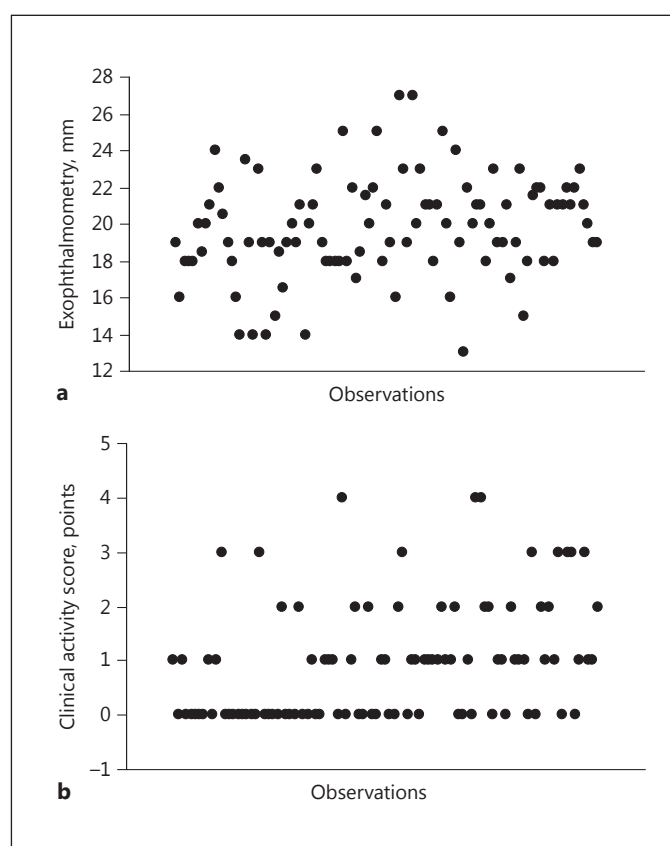
Results

Demographic and clinical features of the cohort are shown in Table 1. GO features at the first and last visit are reported in Table 2a. The cohort included a mixed population of patients with all degrees of GO, from mild to severe, and with a variable activity. Between the first and the last observation, patients received several types of treatment for their thyroid disease and for GO, as indicated in Table 1. Only a minority of patients were untreated. Both exophthalmometry and CAS improved significantly at the last observation, whereas diplopia and visual acuity did not (Table 2a). During the same period in which the 99 patients we studied were observed for the first time, another 37 patients (14 men, 37 women, age 45.8 \pm 11.8 years) were observed for the first time but lost to follow-up in the following years. The eye features of these patients were similar to those of the patients included in the study (Table 2b).

Table 3. Objective criteria for GO disappearance in 99 patients with long-standing (≥ 10 years) eye disease

	All patients	Untreated	Nonsurgical treatment(s)	Surgical treatment(s)	<i>p</i> value
Exophthalmometry (most prominent eye)					
≤ 19 mm in men	15/30 (50)	1/4 (25)	3/13 (23)	11/13 (84.6)	0.008
≤ 17 mm in women	10/69 (14.4)	0/7 (0)	5/37 (13.5)	5/25 (20)	
Clinical activity score $\leq 1/7$	75/99 (75.7)	8/11 (72.7)	38/49 (77.5)	29/39 (74.3)	ns
Absence of diplopia	64/99 (64.6)	6/11 (54.5)	32/49 (65.3)	16/39 (41.0)	
Normal visual acuity or reduction of visual acuity unrelated to GO	96/99 (96.9)	11/11 (100)	47/49 (95.9)	38/39 (97.4)	ns
Normal corneal status	99/99 (100)	11/11 (100)	49/49 (100)	39/39 (100)	ns
No GO-related alterations of the fundi	99/99 (100)	11/11 (100)	49/49 (100)	39/39 (100)	ns
All of the above	8/99 (8.3)	1/11 (9)	5/49 (10.2)	2/39 (5.1)	ns

Values are reported as numbers with percentages in parentheses. GO, Graves' orbitopathy; ns, nonsignificant. *p* values were obtained by χ^2 test

**Fig. 1.** Distribution of exophthalmometry (a) and clinical activity score (b) values at the last observation in 99 patients with long-standing (≥ 10 years) Graves' orbitopathy.

As shown in Table 3, at the last observation, relevant exophthalmos was not observed in 50% of men and $\sim 14\%$ of women, GO was not active based on CAS in $\sim 75\%$ of patients (likely reflecting persistence of activity in the remaining $\sim 25\%$ of patients), there was no diplopia in $\sim 65\%$ of them, and visual acuity was normal in the vast majority ($\sim 97\%$). Finally, the corneal status and the fundi were normal in all patients. However, only 8 patients ($\sim 8\%$) fulfilled all the objective criteria and GO could be considered disappeared. The distributions of exophthalmometry and CAS values at the last observation are shown in Figure 1. In order to determine to what extent the various GO treatments affected the findings, patients were separated into 3 groups: (i) untreated; (ii) nonsurgical treatment(s) (glucocorticoids and/or radiotherapy not followed by surgery); and (iii) surgical treatment(s) (orbital decompression, muscle surgery, palpebral surgery, either alone, associated with, or performed after treatment with glucocorticoids and/or radiotherapy). As shown in Table 3, there was a significant difference concerning the absence of a relevant exophthalmos, which, as somehow expected, was more frequent in patients who had undergone surgical treatment(s) compared with the other 2 groups, likely reflecting orbital decompression. However, GO treatments did not affect CAS, diplopia, visual acuity, corneal status, and fundi. Thus, the prevalence of patients who fulfilled all of the objective criteria for GO disappearance did not differ depending on GO treatment.

As illustrated in Table 4, $\sim 30\%$ of patients believed that their eyes were identical to the way they were before GO appeared and $\sim 43\%$ believed that their eyes were nor-

Table 4. Subjective criteria for GO disappearance in 99 patients with long-standing (≥ 10 years) eye disease

	All patients	Untreated	Nonsurgical treatment(s)	Surgical treatment(s)	<i>p</i> value
Perception of both eyes identical to the way they were before GO appeared	28/99 (28.2)	2/11 (18.1)	15/49 (30.6)	11/39 (28.2)	ns
Perception of both eyes as normal	43/99 (43.4)	2/11 (18.1)	23/49 (46.9)	18/39 (46.1)	ns
No eye-related limitations in daily activities	71/99 (71.7)	9/11 (81.8)	36/49 (73.4)	26/39 (66.6)	ns
No eye-related limitations in social life	85/99 (85.8)	8/11 (72.7)	46/49 (93.8)	31/39 (79.4)	ns
All of the above	24/99 (24.2)	2/11 (18.1)	13/49 (26.5)	9/39 (23.0)	ns

Values are reported as numbers with percentages in parentheses. GO, Graves' orbitopathy; ns, nonsignificant. *p* values were obtained by χ^2 test.

Table 5. Subjective criteria for GO disappearance in 99 patients with long-standing (≥ 10 years) eye disease according to gender

	Men	Women	<i>p</i> value
Perception of both eyes identical to the way they were before GO appeared	13/30 (43.3)	15/69 (21.7)	0.05
Perception of both eyes as normal	18/30 (60)	25/69 (36.2)	0.04
No eye-related limitations in daily activities	27/30 (90)	44/69 (63.7)	0.007
No eye-related limitations in social life	28/30 (93.3)	57/69 (82.6)	ns
All of the above	10/30 (33.3)	14/69 (20.2)	ns

Values are reported as numbers with percentages in parentheses. GO, Graves' orbitopathy; ns, nonsignificant. *p* values were obtained by χ^2 test.

Table 6. Relation between subjective criteria for GO disappearance and age in 99 patients with long-standing (≥ 10 years) eye disease

	Yes	No	<i>p</i> value
Perception of both eyes identical to the way they were before GO appeared	61.2 \pm 11.9	57.6 \pm 10.6	ns
Perception of both eyes as normal	59.6 \pm 10.5	57.8 \pm 11.4	ns
No eye-related limitation in daily activities	58.2 \pm 12.2	56.7 \pm 7.2	ns
No eye-related limitations in social life	58.7 \pm 11.1	58.1 \pm 11	ns
All of the above	60.2 \pm 11.5	58.1 \pm 10.9	ns

Values are reported as mean age in years \pm SD. GO, Graves' orbitopathy; ns, nonsignificant. *p* values were obtained by unpaired *t* test.

mal. The vast majority of patients had no relevant limitations in daily activities ($\sim 72\%$) and social life ($\sim 86\%$). All subjective criteria for GO disappearance were fulfilled in 24 patients ($\sim 24\%$). Again, we separated patients based on GO treatments, but no significant differences were detected concerning all the subjective criteria for GO disappearance (Table 4). As a consequence, the prevalence of patients who fulfilled all the subjective criteria for GO disappearance did not differ between the 3 groups of GO treatment. We considered the possibility that the answers

to the questionnaire may have been influenced by gender and age, which is why we performed additional analyses. As shown in Table 5, the prevalence of patients who believed that their eyes were identical to the way they were before GO appeared, the prevalence of those who believed that their eyes were normal, and the prevalence of those with no relevant limitations in daily activities were significantly greater in men. However, the prevalence of patients with no limitations in social life and the prevalence of those in whom all the subjective criteria for GO

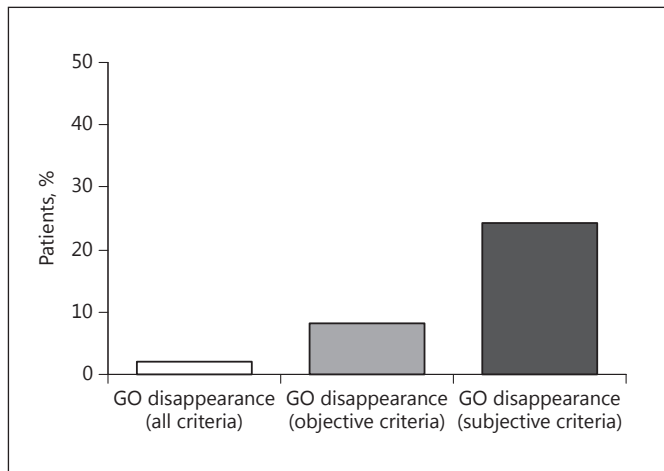


Fig. 2. Prevalence of Graves' orbitopathy (GO) disappearance based on objective and subjective criteria or both in 99 patients with long-standing (≥ 10 years) eye disease. Objective criteria: (i) exophthalmos ≤ 19 mm in men and ≤ 17 mm in women; (ii) clinical activity score $\leq 1/7$ points; (iii) absence of diplopia; (iv) normal visual acuity, or reduction of visual acuity unrelated to GO; (v) normal corneal status; and (vi) no GO-related alterations of the fundi. Subjective criteria (questionnaire): (i) perception of both eyes identical to the way they were before GO appeared; (ii) perception of both eyes as normal; (iii) no eye-related limitations in daily activities; and (iv) no eye-related limitations in social life.

disappearance were fulfilled were not affected by gender. None of the answers to the questionnaire was affected by age (Table 6).

When we considered altogether the subjective criteria reported in Table 3 and the objective criteria reported in Table 4, only 2 patients ($\sim 2\%$) had all criteria fulfilled and could be considered as GO-free (Fig. 2). One of these 2 patients had been treated with oral glucocorticoids and the other with intravenous glucocorticoids and radiotherapy. No surgical treatments had been performed in these patients.

Discussion

In the present perspective study, we showed that GO is overall a chronic disease which disappears only in a minority of patients. We examined the issue from both the clinician's point of view, namely by ophthalmological evaluation, and the patient's self-assessment. In this study, we investigated all consecutive GO patients who came for a follow-up visit in our GO clinic over a period of 5 years and who had a GO history of at least 10 years.

The results supporting our conclusions can be summarized as follows.

Only 2 of 99 patients, namely $\sim 2\%$ of a total cohort of 99 subjects, had no relevant GO signs by ophthalmological evaluation and gave positive answers to a questionnaire on GO persistence, namely they believed that their eyes were identical to the way they were before GO appeared and that their eyes were normal, and they had no relevant limitations in daily activities and social life. Based on objective criteria, GO could be considered absent in $\sim 8\%$ of patients. Interestingly, in spite of the persistence of GO signs by ophthalmological examination in most patients, $\sim 24\%$ of them believed that they no longer had GO, which probably reflects some sort of psychological adaptation to the changes in appearance or to the functional limitations related to GO.

GO treatments did not seem to affect the disappearance of GO. Thus, besides an expected greater proportion of patients with no relevant exophthalmos after surgical treatments, mainly orbital decompression, all the remaining objective criteria and all the subjective criteria for GO disappearance did not differ based on GO treatment. The proportion of untreated patients in which GO disappeared was 9% based on objective criteria and $\sim 24\%$ based on subjective criteria, but none of the 11 untreated patients fulfilled both criteria. Findings are in apparent contrast with those of a study by Tanda et al. [8], in which 58% of patients were reported to have a complete remission of GO. The discrepancy may be explained by the fact that patients in that study had a mild GO [8], whereas the majority of patients in our study had a moderate-to-severe GO, thereby making the 2 populations difficult to compare. In addition, the study by Tanda et al. [8] was performed in a secondary referral center, where patients are more likely to receive a prompt treatment for both hyperthyroidism and ophthalmopathy, with anti-thyroid drugs and/or selenium [22–25], which may result in an overall better GO outcome in the long term and in the prevention of GO deterioration over time. In contrast, our study was performed in a tertiary referral center, where most patients are seen long after the initial diagnosis, and may not have received a prompt initial treatment. In this regard, our findings probably reflect the long-term outcome of moderate-to-severe GO but may not necessarily apply to all degrees of GO.

To our knowledge, only 2 previous studies with a follow-up of sufficient duration examined the issues investigated here. In the first one, Bartley et al. [19] examined 120 patients with GO who had a median follow-up time of 9.6 years. A follow-up longer than 10 years was avail-

able in 59 patients. Patients were investigated by survey (a telephone interview), and ~40% of respondents believed that their eyes had returned the way they were before GO appeared, a proportion slightly greater than the one we obtained in the present study (~28%). In the same study [19], ~45% of patients believed that their eyes appeared “normal,” which is very much in line with our observation (~43%). The issue of treatment was not considered by Bartley et al. [19], thus, it is not clear whether the findings reflected a response to treatment or the natural history of GO. Here we did not find any relationships between the disappearance of GO, both objective and subjective, and the various thyroid and eye treatments which patients had undergone. In 2002, Terwee et al. [20] performed a long-term follow-up study (with a median GO duration of 11.7 years) in 164 GO patients, both by clinical examination (154 patients) and questionnaire (all patients). In their study, the proportion of patients who believed that their eyes had returned to normal was not evaluated, nor was the overall presence/absence of GO signs and symptoms. However, the authors evaluated the single GO features and found that: (i) ~10% of patients had no soft tissue involvement in the long term; (ii) no patients had an exophthalmos <21 mm; (iii) 6% of patients had a lid aperture <9 mm; and (iv) 25% of patients had a CAS between 0 and 1. Overall, the findings are in contrast with our observations. Thus, we found an exophthalmos below the upper limit for gender in ~25% of patients and a CAS between 0 and 1 in the vast majority of patients (~76%). In the study by Terwee et al. [20], the severity of GO before treatment was apparently greater than that in patients of our series, which may explain the discrepancies. In the SF-36 health survey [26], all of the GO patients in the study by Terwee et al. [20] had a Z-score below 0 for all the features under examination, except for bodily pain, suggesting the persistence of GO. In addition, the mean EuroQol score on quality of life [27] was lower than that of a reference, normal, population. Thus, as in our study, overall, the findings seem to indicate that GO disappears very rarely and that patients’ eye do not usually return to how they were before GO appeared.

A possible limitation of our study, and probably also of the previous studies on the same issue [19, 20], is that some patients in whom GO had actually disappeared may have been lost to follow-up. Thus, patients who did not have GO anymore may have decided not to attend regular visits in our GO Clinic and, therefore, the overall prevalence of GO disappearance may have been underestimated. In this regard, 37 additional patients who were observed in our Clinic for the first time in the very same

period of patients of the present study were lost to follow-up. The eye features of these patients were similar to those of the 99 patients who were included in the study. This somehow militates against the possibility that these 37 patients lost to follow-up had a GO outcome different from that of the 99 patients included in the study, although obviously we cannot exclude with certainty that some of them did not attend regular visits because their GO had disappeared.

As mentioned above, the number of studies on GO disappearance is rather limited, which is why there are no established criteria to determine whether GO has disappeared or not, both from the objective and subjective points of view. Concerning the first, it may be argued that the criteria we used were too strict. For example, an exophthalmos ≥ 19 mm in men or ≥ 17 mm in women may be observed in otherwise normal subjects. However, several studies have shown that exophthalmometry values in normal subjects are on average 15 ± 1 mm [14–18], with higher values in men than in women. Thus, the cutoff values we arbitrarily establish should reflect the normal values of the general population plus two standard deviations. On the same line, intermittent diplopia may not be a significant measure of persistence of GO. However, in our patients intermittent diplopia was observed at the last observation only in 4 of 99 patients, and in none of these 4 patients was it the only sign of GO persistence. Concerning the disappearance of GO according to subjective criteria, again there are no established values or questionnaires. Thus, the questionnaire we administered to patients was basically the same used by Bartley et al. [19], which, to our knowledge, was not validated for age and gender. In this regard, it may be argued that these variables may have affected the answers of patients. When we analyzed the distribution of the answers based on gender, some of the indicators of GO disappearance (perception of both eyes identical to the way they were before GO appeared, perception of both eyes as normal, no eye-related limitations in daily activities) were more frequent in men, likely reflecting a different psychological attitude between genders towards the eye disease, especially concerning physical appearance. In this regard, women may have overestimated their GO symptoms or, in contrast, men may have underestimated theirs. However, these differences did not seem to affect the overall findings concerning both disappearance of GO according to all subjective criteria and disappearance of GO according to both subjective and objective criteria. Thus, when subjective criteria were considered altogether, no significant difference between men and women was detected. No age-related

differences were observed, indicating that the questionnaire was not affected by age. The possibility remains that, to some extent, patients responded positively to the questionnaire to please their doctors, which however, is unlikely to be the case, as indicated by the overall low proportion of patients who believed that their GO was no longer present.

The general impression that comes from our and previous studies is that the eyes of GO patients do not return to normal even after a very long time since the disease appear-

ance from the physician's point of view, although a discrete proportion of patients feel so. The available data suggest that GO is generally a long-lasting, chronic disease. In our opinion, this information is to be taken into account in the clinical practice regarding patient counseling.

Disclosure Statement

The authors have no conflict of interest.

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